From the DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

SUDDEN UNEXPECTED DEATH IN EPILEPSY, INCIDENCE, CIRCUMSTANCES AND RISK FACTORS

Olafur Sveinsson

Stockholm 2020

Institutionen för klinisk neurovetenskap

SUDDEN UNEXPECTED DEATH IN EPILEPSY, INCIDENCE, CIRCUMSTANCES AND RISK FACTORS

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Eugeniasalen, T3, Karolinska universitetssjukhuset Solna, 171 76 Stockholm

Fredagen den 13 mars 2020, kl 09.00

av
Olafur Sveinsson
Läkare

Cover page, Madonna by Sveinn Björnsson, Sveinssafn
Published by Karolinska Institutet.
Printed by Universitetsservice US-AB

ISBN 978-91-7831-695-3

SUDDEN UNEXPECTED DEATH IN EPILEPSY, INCIDENCE, CIRCUMSTANCES AND RISK FACTORS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Olafur Sveinsson

Principal Supervisor:
Professor Torbjörn Tomson
Karolinska Institutet
Department of Clinical Neuroscience

Co-supervisors:
Associate Professor Sofia Carlsson
Karolinska Institutet
Institute of Environmental Medicine

Associate Professor Peter Mattsson
Uppsala University
Department of Neuroscience

Opponent:
Professor Eylert Brodtkorb
Norwegian University of Science and Technology,
Trondheim, Norway

Examination Board:
Professor Anne-Marie Landtblom
Uppsala Universtity
Department of Neuroscience

Associate Professor Susanna Larsson
Uppsala university
Department of Surgical Sciences
Karolinska Institutet
Institute of Environmental Medicine

Associate Professor Jonatan Salzer
Umeå University
Department of Clinical Neuroscience

To Inga

Next to selfishness, the principal cause that makes life unsatisfactory is lack of mental cultivation. John Stuart Mill (Utilitarianism 1861)

ABSTRACT

Although Sudden Unexpected Death in Epilepsy (SUDEP) has attracted increasing attention from the scientific community during the last 20 years, important gaps in knowledge still exist that hamper the development of methods aiming at prevention of this, the most devastating consequence of epilepsy. We are still missing large population-based studies on the incidence of SUDEP. Our understanding of the circumstances surrounding SUDEP is incomplete which is a major limitation when it comes to development of potential SUDEP-preventing devices. Finally, our understanding of risk factors for SUDEP is limited to a few established risk factors. The purpose of this study was to examine the incidence, circumstances and risk factors for SUDEP in Sweden.

The project is based on a study population (n=78 524) which comprises all persons living in Sweden at 1. July 2006, who at some point during 1998-2005 where registered with the diagnosis code for epilepsy (ICD G 40) in the Swedish National Patient Register (SNPR). To identify cases of SUDEP, the study population was linked to the National Cause-of-Death Register. During the follow-up time from July 1, 2006 to December 31, 2011, we identified 9605 deaths. All death certificates in the study population between 1 July 2006 and 31 December 2011 with epilepsy mentioned on death certificate and all deaths during 2008 (n=3166) were reviewed. Based on the information in the death certificates, obvious non-SUDEP deaths were excluded from further analysis. For all others we analyzed patient medical records, autopsy and police reports and information was extracted using a standardized protocol. From the study population, five epilepsy controls per SUDEP case, of the same sex, who were alive at the case´s time of death, were randomly selected by the National Board of Health and Welfare.

During 2008, 1890 individuals from the study population died. Of these, 99 met Annegers' SUDEP criteria (49 definite, 19 probable, and 31 possible) (paper I). Definite and probable SUDEP accounted for 3.6% of all deaths in the study population during 2008, and 5.2% when possible was included. In the age group 0-15 years, the relative contribution of SUDEP (definite, probable and possible) to overall deaths was 36.0%. SUDEP incidence was 1.20/1000 person-years (definite/ probable) and 1.74/1000 if possible SUDEP was included. Epilepsy was mentioned in any position of the death certificate in 63.6% of the 99 SUDEP cases.

Of the 329 SUDEP deaths identified from July 1, 2006 to December 31, 2011 (167 definite, 89 probable, 73 possible), more than half (58%) occurred at night and 91% died at home, whereof 65% were found deceased in bed (paper II). Death was witnessed in 17% of all SUDEP cases and when a seizure was witnessed in conjunction with SUDEP (n=49) all were generalized tonic-clonic seizures (GTCS). Where a body position was documented

(43%), more than two thirds (70%) were found prone. Dying at night made it more likely (80%) to be found prone than other times (55%) ($p<0.001$). Among adult SUDEP cases, 75% were living alone, and only 14% of all SUDEP cases shared a bedroom.

In papers III and IV, 255 SUDEP cases (167 definite, 88 probable) were compared to their matched 1148 controls. Those with a history of GTCS had a tenfold increased SUDEP risk and the risk was increased to 32-fold with 4-10 GTCS during the last year of observation. When a history of nocturnal GTCS was present, a nine-fold SUDEP risk was observed and a 15-fold risk was seen if nocturnal GTCS were present during the last year of observation. No increased risk of SUDEP was seen in those experiencing exclusively non-GTCS during the preceding year. There was a fivefold increased risk of SUDEP among those living alone, while the risk was reduced to twofold when sharing household but not bedroom. Individuals experiencing ≥1 GTCS and not sharing a bedroom with someone had 67-fold increased risk of SUDEP compared to individuals not having GTCS, who shared their bedroom with someone, with attributable proportion due to interaction estimated at 0.69 (95% confidence interval, CI 0.53-0.85). Polytherapy, especially taking three or more AEDs was associated with a 69% reduced SUDEP risk after adjusting for GTCS frequency and other covariates. Levetiracetam as monotherapy was associated with a significantly lower SUDEP risk when compared to no AED treatment (odds ratio, OR 0.10, 95% CI 0.03-0.61). Lamotrigine, valproic acid and levetiracetam were associated with a significantly reduced risk when used as part of a polytherapy. Use of statins was associated with a reduced risk of SUDEP (OR 0.34, 95% CI 0.11-0.99).

Our results show that SUDEP is an important contributor to mortality in epilepsy patients, and accounts for one third of deaths in children with epilepsy and one fifth of deaths among young adults with epilepsy. Since the majority died at home in bed, at night with indications of a previous GTCS, SUDEP can be considered an event related to night time and unobserved GTCS. We found no excess risk of SUDEP among individuals experiencing non-GTCS only, which has important clinical implications. GTCS and lack of supervision were the main risk factors. Moreover, our results suggest that up to 69% of SUDEP cases could be prevented in individuals with GTCS who live alone, if they were made free from GTCS or did not sleep alone. Polytherapy was associated with a substantially reduced SUDEP risk indicating that physicians should to consider AED polytherapy more pro-actively for patients with poorly controlled GTCS.

SAMMANFATTNING PÅ SVENSKA

Epilepsi är det vanligaste allvarliga kroniska neurologiska sjukdomstillståndet med en prevalens på 6- 7/1 000. Epilepsi kan ha allvarliga konsekvenser. Av särskild vikt är förhöjd mortalitet, 2 – 3 gånger högre än förväntat och därav påtagligt förkortad livslängd. Den förhöjda mortaliteten förklaras delvis av underliggande orsaker till epilepsi såsom hjärntumörer och cerebrovaskulär sjukdom men är också delvis en konsekvens av anfallssjukdomen. Plötslig oväntad död, sudden unexpected death in epilepsy (SUDEP), anses vara den främsta epilepsirelaterade dödsorsaken. Plötslig död är 20 gånger vanligare hos personer med epilepsi jämfört med befolkningen i allmänhet. Även om SUDEP har fått ökad uppmärksamhet under de senaste 20 åren, finns det fortfarande stora kunskapsluckor. Syftet med avhandlingen har varit att ta fram ny kunskap om förekomst, riskfaktorer och omständigheter runt SUDEP, med det övergripande målet att skapa bättre underlag för framtida åtgärder för att förhindra denna förödande konsekvens av epilepsi.

Målet med delarbete I var att identifiera alla fall av SUDEP i Sverige under ett år. Vi inkluderade alla individer med epilepsidiagnos i svenska patentregistret under 1998–2005 och som var vid liv den första januari 2008. Av dessa 57 775 personer hade 1890 (3,3%) avlidit under 2008. 99 uppfylllde kriterierna för SUDEP som stod för 5,2% av alla dödsfall bland personer med epilepsi och 36% av dödsfallen i åldersgruppen 0-15 år. Förekomsten av s.k. definite/probable SUDEP var 1,20/1000 personår, vilket är i linje med tidigare rapporeer. Att risken var ungefär lika stor bland barn som bland vuxna är emellertid en ny observation. Epilepsi nämndes någonstans på dödsorsaksintyget hos 64% av all SUDEP-fall. Sammanfattningsvis visade studien att SUDEP står för en betydande andel av alla dödsfall hos epilepsipatienter och dödsorsaksintyg inte är en tillräckligt känslig metod för att upptäcka SUDEP fall.

Syftet med delarbete II var att analysera omständigheterna kring SUDEP. Studiepopulationen bestod av alla individer med epilepsidiagnos i det svenska patientregistret från 1998–2005, som var vid liv den 30 juni 2006 (n = 60 952). Vi identifierade 329 SUDEP fall under uppföljningsperioden 1 juli 2006 t.o.m. 31 december 2011. Hos 17% var dödsfallet bevittnat och hos 88% av dessa observerades ett epileptiskt anfall i samband med dödsfallet, alla dessa hade ett generaliserat tonisk-kloniskt anfall. De flesta SUDEP-fallen bodde ensamma och endast 14% delade sovrum. Jämfört med en referensgrupp bestående av personer med epilepsi som avlidit av andra fastställda orsaker än SUDEP, avled de s.k. definite SUDEP oftare hemma, under natten, obevittnade, och hittades oftare liggande på magen. De var också vanligare att SUDEP-fallen var ensamboende och att de uppvisade tecken på föregående anfall. Observationerna indikerar att brist på tillsyn är en vanlig omständighet vid SUDEP och detta bör beaktas vid utveckling av förebyggande strategier.

I delarbete III genomförde vi en landsomfattande fallkontrollstudie för att testa hypotesen

att vissa specifika kliniska riskfaktorer är förknippade med ökad risk för SUDEP. Studien inkluderade 255 SUDEP-fall (definite och probable) och 1148 matchade kontroller, epilepsipatienter som inte avlidit. Studien visade att förekomst av generaliserade tonisk-kloniska anfall (GTCS) under året före döden var förknippat med en 27-faldigt ökad SUDEP risk. Ingen ökad risk observerades hos personer med epileptiska anfall som inte var av typen GTCS. Nattliga GTCS under observationsåret var förknippade med en 15-faldig riskökning och att leva ensam var associerat med en femfaldigt ökad risk för SUDEP. Interaktionsanalys visade att kombinationen av att inte dela sovrum och att ha GTCS var förenat med en 67-faldigt ökad risk för SUDEP. Resultaten indikerar att 69% av SUDEP-fall som har GTCS och bor ensamma skulle kunna förhindras om de inte var obevakade på natten eller var fria från GTCS.

I delarbete IV användes samma fall och kontroller som i arbete III för att studera sambandet mellan användning av antiepileptika (AEDs), och andra potentiellt relevanta läkemedel och SUDEP-risk. Polyterapi (minst två AED givna i kombination) var associerad med en minskad risk för SUDEP, även efter justering för anfall, levnadsvanor och ett stort antal andra möjliga riskfaktorer. Inget AED, vare sig i mono- eller polyterapi, var associerat till ökad risk för SUDEP. Levetiracetam var den enda monoterapin som var associerad med en statisitiskt signifikant reducerad SUDEP-risk. Vi observerade ingen ökad eller minskad risk för SUDEP i samband med behandling med SSRI, andra antidepressiva, neuroleptika eller beta-blockerare. Däremot fanns en minskad risk för SUDEP bland personer som använde statiner. Våra resultat tyder på att AEDs kan ha en skyddande effekt utöver de anfallskontrollerande egenskaperna.

LIST OF SCIENTIFIC PAPERS

I. **Sveinsson O**, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. Neurology 2017;89(2):170-177.

II. **Sveinsson O**, Andersson T, Carlsson S, Tomson T. Circumstances of SUDEP: A nationwide population-based case series. Epilepsia 2018;59(5):1074-1082.

III. **Sveinsson O**, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. Neurology 2020;94:e419-e429.

IV. **Sveinsson O**, Andersson T, Mattsson P, Carlsson S, Tomson T. Pharmacological treatment and SUDEP risk: a nationwide population-based case-control study. Submitted.

CONTENTS

LIST OF ABBREVIATIONS

AAN	American Academy of Neurology
AED	Antiepileptic drug
AES	American Epilepsy Society
AP	Attributable to interaction
CI	Confidence interval
CNS	Central nervous system
CT	Computerized tomography
EEG	Electroencephalogram
GTCS	Generalized tonic-clonic seizures
ICD	International classification of disease
ILAE	International League Against Epilepsy
MRI	Magentic resonance imaging
PGES	Postictal generalized EEG suppression
OR	Odds ratio
RR	Rate ratio
SSRI	Selective serotonin reuptake inhibitor
SMR	Standardized mortality ratio
SCD	Sudden cardiac death
SIDS	Sudden infant death syndrome
SUDEP	Sudden unexpected death in epilepsy
VNS	Vagus nerve stimulation

1 INTRODUCTION

Epilepsy is among the oldest recognized diseases and narrations date back to Mesopotamian writings (Kinnear 1990). The word, epilepsy, derives from the Greek meaning ‘’to take hold’’. Epilepsy is one of the most common serious chronic neurological conditions with a prevalence of 0.6-0.7% affecting both sexes and all ages and with a worldwide distribution (Murray et al., 2012). At least 50 million individuals have epilepsy worldwide (Ngugi et al., 2010). Epilepsy has been ranked by the 2010 Global Burden of Disease study as the second most burdensome neurological disorder regarding disability-adjusted life years (DALYs) (Murray et al., 2012). This is partly due to a reduced life expectancy (Thurman et al., 2014, Thurman et al., 2017). The increased mortality among people with epilepsy relates to the underlying causes of epilepsy but can also be a consequence of the epilepsy and the seizures (Tomson et al., 2008; Thurman et al., 2014; Thurman et al., 2017). Death is well recognized in the context of a long-standing seizure, status epilepticus, but uncommon in conjunction with a seizure of normal duration. With this said, individuals with epilepsy are sometimes found dead, often in bed, despite having been under good health during the preceding days. When documented status epilepticus, trauma, and drowning have been excluded, and a post-mortem examination does not reveal a structural or toxicologic cause for death, this is called Sudden Unexpected Death in Epilepsy (SUDEP) (Nashef, 1997). When SUDEP is witnessed, a preceding major convulsive seizure is observed in around 90% of cases and the patient dies in the aftermath of the seizure (Tomson et al., 2008). Despite increased attention over the last three decades and being the major epilepsy related cause of death (Thurman et al., 2014; Devinsky et al., 2016a), there is still uncertainty regarding the mechanisms, incidence and risk factors of SUDEP.

2 BACKGROUND

2.1 DEFINITIONS AND CLASSIFICATION OF SEIZURES AND EPILEPSY

2.1.1 Definition of seizures

Epileptic seizures are the cardinal manifestations of epilepsy and are recurrent paroxysmal events characterized by stereotyped behavioral alterations reflecting the neural mechanisms involved in the epileptic process (Fisher et al., 2005). An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al., 2005; Fisher et al., 2017a).

2.1.2 Classification of seizures

Based on the initial manifestations, seizures are classified into focal, generalized or unknown onset (Fisher et al., 2017a). Seizures are labelled focal when the epileptic activity is originated within networks limited to one hemisphere, and seizures are considered generalized when the epileptic activity has arisen in or rapidly engaged bilaterally distributed networks (Fisher et al., 2017a). Based on impact on awareness focal seizures are subdivided into focal aware and focal unaware, respectively. A focal seizure may evolve to a bilateral tonic-clonic seizure and is then named focal to bilateral tonic-clonic seizure (FBTCS) in the new classification system (Fisher et al., 2017b). Generalized seizures are subdivided further into: tonic-clonic, clonic-tonic, absences, myoclonic and atonic seizures. If there is insufficient evidence to characterize the seizure as focal or generalized it is labelled unknown (Fisher et al., 2017a). A schematic view of this new classification of seizures can be seen in figure 1.

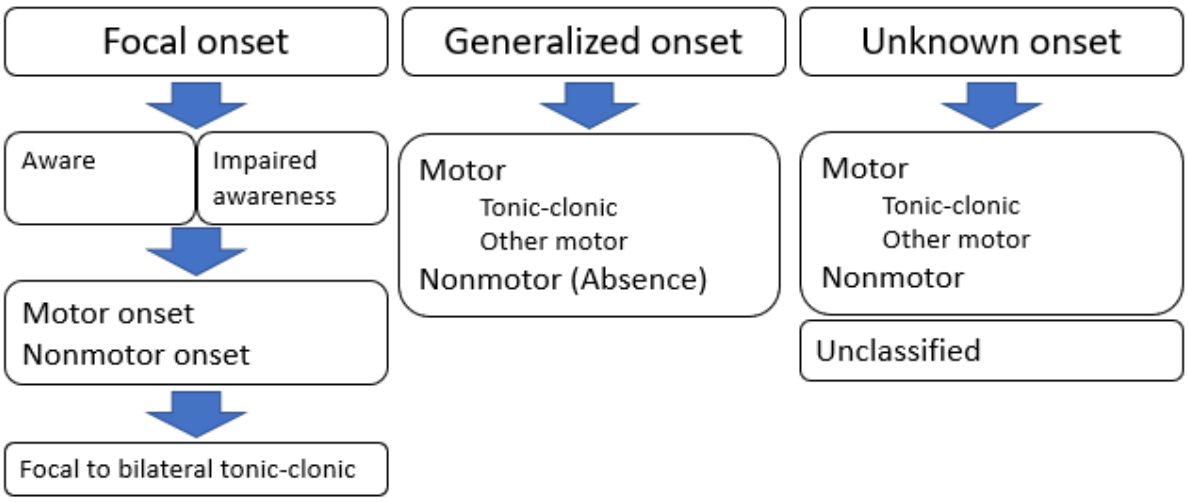

Figure 1. ILAE 2017 Classification of Seizure Types Basic Version

2.1.3 Definitions of Epilepsy

Since 2005, the International League against Epilepsy (ILAE) has defined epilepsy conceptually as: "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition". The definition of epilepsy requires the occurrence of at least one epileptic seizure (Fisher et al., 2005). Traditionally epilepsy has been defined clinically as the occurrence of two unprovoked seizures (Hauser et al., 1996) but since 2014 the ILAE has defined epilepsy in practical clinical terms as a "disease of the brain followed by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome" (Fisher et al., 2014).

Not all individuals who experience seizures have epilepsy. Seizures occurring in close proximity of an acute CNS injury or a metabolic, toxic or pharmacological disturbance, are termed *provoked* or *acute symptomatic seizures.* The distinction between unprovoked and

acute symptomatic seizures is important, since the risk of recurrence of the latter is low once the acute phase of the CNS insult is over or the metabolic/toxic derangement is resolved (Hesdorffer et al., 2009; Beghi et al., 2010). Hence, this situation does not represent an "enduring predisposition" to generate seizures which is the hallmark of epilepsy.

2.1.4 Classification of epilepsy

The ILAE classification of the epileptic seizures and the epilepsies has been updated following scientific advances on the underlying mechanisms that have taken place in the last decades (Fisher et al., 2017a; Scheffer et al., 2017). Epilepsy types, previously called localization-related, generalized, or undetermined, are now divided into focal, generalized, combined generalized and focal or unknown (figure 2) primarily based on the types of seizures in the individual patient (Scheffer et al., 2017). Regarding classification of causes of epilepsy, the previous terms symptomatic, idiopathic and cryptogenic have been replaced by six etiological categories which are not mutually exclusive: genetic, structural, immune, infectious, metabolic, and unknown (Scheffer et al., 2017) (figure 2).

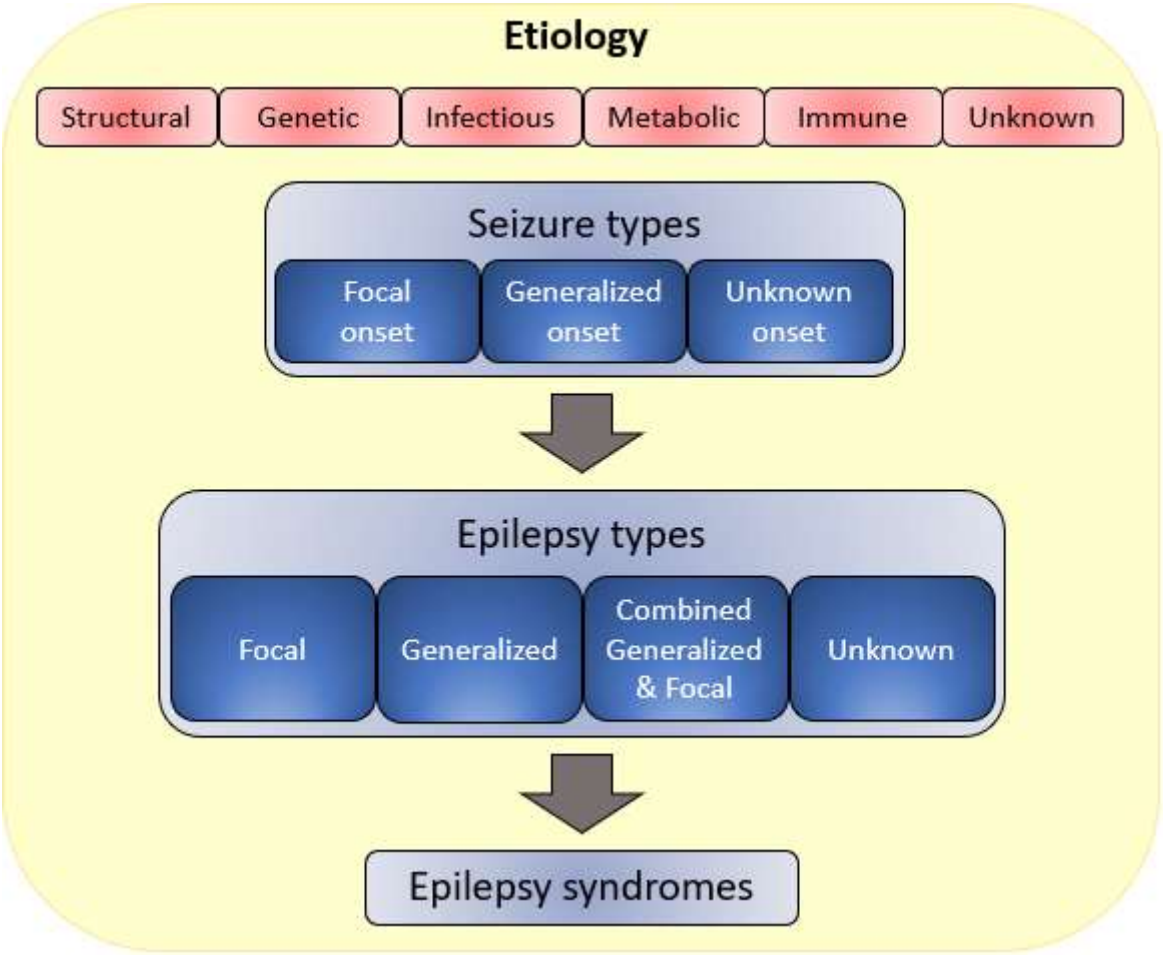

Figure 2. ILAE 2017 Classification of the epilepsies

2.2 INCIDENCE AND PREVALENCE OF EPILEPSY

The incidence of epilepsy varies from 24 to 71 per 100,000-person years in high income countries up to 190 per 100,000 in low/middle income countries (Forsgren et al., 2005; Ngugi et al., 2011; Singh and Trevick, 2016; Fiest et al., 2017). In a meta-analysis the incidence was 61.4 per 100,000 person-years (48.9 per 100,000 person-years in high income countries and 139.0 in low/middle income countries, respectively) (Fiest et al., 2017). In Sweden, the incidence of an unprovoked seizure was measured to be 56 per 100,000 person-years among adults and 89 among children in the county of Västerbotten (Sidenvall et al.,1993; Forsgren et al., 1996). In northern Stockholm the incidence of a first unprovoked seizure and epilepsy was 33.9/100,000 person-years, where the moderately lower incidence can be explained by under-ascertainment, particularly among the elderly (Adelöw et al., 2009). The higher

incidence in low/middle-income countries may be explained by a greater exposure to perinatal risk factors, infections and traumatic brain injury and the different age structure of the populations at risk. The incidence of epilepsy is marginally higher in men, both in high income and in low/middle-income countries (Fiest et al., 2017). Around 4000-5000 individuals are diagnosed with epilepsy in Sweden every year, which corresponds to a new patient every second hour (Forsgren et al.,2018). The incidence of epilepsy is highest at the extremes of the age. Over the last decades, age-specific incidence of epilepsy has decreased in the youngest age groups and increased in the older age groups (Forsgren et al., 2005; Singh et al., 2016). This could partly be explained by the improvement of perinatal care and the control of infectious diseases while the increased incidence during older age could be caused by increased life expectancy with an associated increase in epilepsy related diseases such as degenerative CNS disorders and stroke.

The prevalence of active epilepsy varies from 4 to 8 per 1,000 inhabitants in high income countries. A population-based study in a Norwegian county showed that 0.65% of the population had active epilepsy (Syvertsen et al., 2015). In a meta-analysis of international studies, the point prevalence was 6.4 per 1,000 inhabitants (5.5 in high income countries) and lifetime prevalence 7.6 per 1,000 (Fiest et al., 2017). Active epilepsy is often defined as epilepsy with unprovoked epileptic seizures over the past five years or ongoing antiepileptic medication regardless of the time since last seizure (Forsgren et al., 2018). In 1985 the prevalence of active epilepsy in northern Sweden was 0.58% (Forsgren, 1992). Today, 60,000 to 70,000 people are thought to have active epilepsy in Sweden. Of these, just over 10,000 are children and over 50,000 are adults (Forsgren et al., 2018).

2.3 SEIZURE CONTROL

The prognosis regarding seizure control has been suggested to fall into four different categories (Sander, 1993) and is relatively favorable in the majority of patients. One group (20-30%) has an excellent prognosis with high probability of spontaneous remission. In the second group, 30-40% will achieve remission with relatively simple pharmacological treatments and some will go in to spontaneous remission. In the third group (10-20%), the prognosis is uncertain. Here, the patient often responds to antiepileptic drugs (AEDs) but tends to relapse after treatment withdrawal. In the fourth group (20%) the prognosis is poor, and seizures persist despite extensive treatment efforts.

The strongest prognostic predictor for seizure control under AED treatment is the etiology behind the epilepsy. Seizure remission is less common among patients with known or presumed etiology (Beghi et al., 2015). Individuals with neurological injury from birth have the lowest chance of achieving remission (Beghi et al., 2015. Those without epileptiform abnormalities on EEG and/or absence of GTCS have a higher likelihood of remission at 5 years (Beghi et al., 2015). In a long term follow up study of children who were diagnosed with epilepsy in Turku, Finland between 1961-1964, 64% had been seizure free for the last five years in 1992. Predictive factors for seizure freedom were early response to AEDs and having idiopathic epilepsy (presumed genetic epilepsy) (Sillanpää et al., 1998). Recognizing that a significant proportion of people with epilepsy will eventually become seizure free and able to withdraw their medication without relapses, the ILAE has introduced the term *epilepsy resolved* for those who have been seizure-free for 10 years and without any AEDs during the last five years (Fisher et al., 2014).

2.4 MORTALITY IN EPILEPSY

According to WHO, epilepsy is estimated to contribute 0.5% of world total "burden of disease" in terms of disability-adjusted life years (DALYs), which is comparable with psychotic disorders, Alzheimer's and other dementias (WHO 2000). This is partly attributed to the serious consequences of epilepsy. Of particular importance is the high mortality rate, 2 - 3 times higher than expected (Nilsson et al., 1997; Mohanraj et al., 2006) and hence the significantly shortened lifespan. In a recent systematic review in high income countries (Thurman et al.,2017), the weighted standardized mortality ratio (SMR) in six population-based studies was 2.3. The elevated mortality can be explained in part by the underlying causes of epilepsy such as brain tumors and cerebrovascular disease but may also be a consequence of epilepsy related deaths including seizure related accidental deaths, drownings, but also suicide in people with epilepsy (Fazel et al., 2013). Sudden Unexplained Death in Epilepsy (SUDEP) is the leading epilepsy-related cause of death (Tomson et al., 2008; Thurman et al., 2014; Thurman et al., 2017). Among neurological diseases, SUDEP ranks only second to stroke in terms of potential years of life lost (Thurman et al., 2014). The risk of sudden unexpected death has been estimated to be 24-28-fold higher among young people with epilepsy than in the general population (Ficker et al., 1998; Holst et al., 2013). The cumulative lifetime risk of SUDEP differs according to age of epilepsy onset. In a model based on data from population-based studies, the lifetime risk for SUDEP (up to 70 years of age) has been estimated to 8.0% if epilepsy has its onset at 1 year of age, 7.2% with onset at 15 years and 4.6% with onset of epilepsy at 30 years of age (Thurman et al., 2014). In the cohort from Turku in Finland cited above, 60 individuals, 24% of the study population had died 40 years after diagnosis, which was three times more than expected. Of the 60 deaths, 18 individuals had died due to SUDEP where the risk was higher in those still having seizures (Sillanpää and Shinnar 2010).

2.5 SUDDEN UNEXPECTED DEATH IN EPILEPSY

2.5.1 Background, definitions, and classification

Already in 1904, Spratling described epilepsy as a disease that: "destroys life suddenly and without warning through a single, brief attack...and does so in from 3 to 4% of all who suffer from it" (Spratling 1904). When Spratling describes it as a brief attack, SUDEP comes to mind. Despite awareness of the condition, it was not until some 20 years ago that more generally accepted definitions and classifications of SUDEP were introduced (Nashef, 1997; Annegers, 1997). Accordingly, SUDEP is generally defined as "the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicologic cause for death''(Nashef, 1997). Annegers suggested that cases fulfilling the above definition fall into the "definite SUDEP" category; sudden deaths occurring in benign circumstances with no known competing cause for death but without autopsy are classified as "probable SUDEP" (Annegers, 1997). Cases where SUDEP cannot be excluded, either because of limited information regarding death circumstances or there is a plausible competing explanation for death are classified as "possible SUDEP" (Annegers, 1997). Since then, modifications have been suggested to allow for more refined classification of cases (Nashef et al., 2012). The previously definite, probable and possible were unchanged but the category "definite SUDEP plus" was introduced for cases that fulfill the definition of definite SUDEP but where there is a concomitant condition (identified before or after death) that could contribute to the sudden death. The death may have been due to a combined effect of both conditions, and investigations do not confirm the concomitant condition to be the cause of death. The same applies to "Probable SUDEP plus" where a postmortem is missing. If an individual with epilepsy survives resuscitation for more than one hour after a cardiorespiratory arrest that has no structural cause identified after investigation, the term near-SUDEP was suggested (Nashef et al., 2012).

2.5.2 Proposed mechanisms

The pathophysiology of SUDEP is unknown, however, it is thought to be a combination of a seizure induced ictal and post-ictal brainstem, respiratory, and cardiac dysfunction where the seizure in most cases seems to be a focal to bilateral tonic-clonic seizure (FBTCS) (Ryvlin et al., 2019). Despite being separate seizure types, no distinction has been made in the SUDEP literature between a tonic-clonic seizure evolving from a focal or with a generalized onset. Henceforth in this work both types will be referred to as GTCS. Clinical observations demonstrate that SUDEP is preceded by a GTCS in the vast majority of cases, but it is unclear by which mechanisms seizures may cause SUDEP and the mechanisms can be heterogenous (Tomson et al., 2008; Ryvlin et al., 2019). Three main hypotheses have been put forward but the cause is likely most often a combination: a) cardiac arrhythmia or other cardiac dysfunction triggered by a seizure or b) respiratory failure triggered by a seizure, or c) a seizure triggered cancellation of cerebral activity (electro-cerebral shut-down) and subsequent failure of arousal (Tomson et al., 2008; Richerson et al., 2016; Ryvlin et al., 2019) (figure 3).

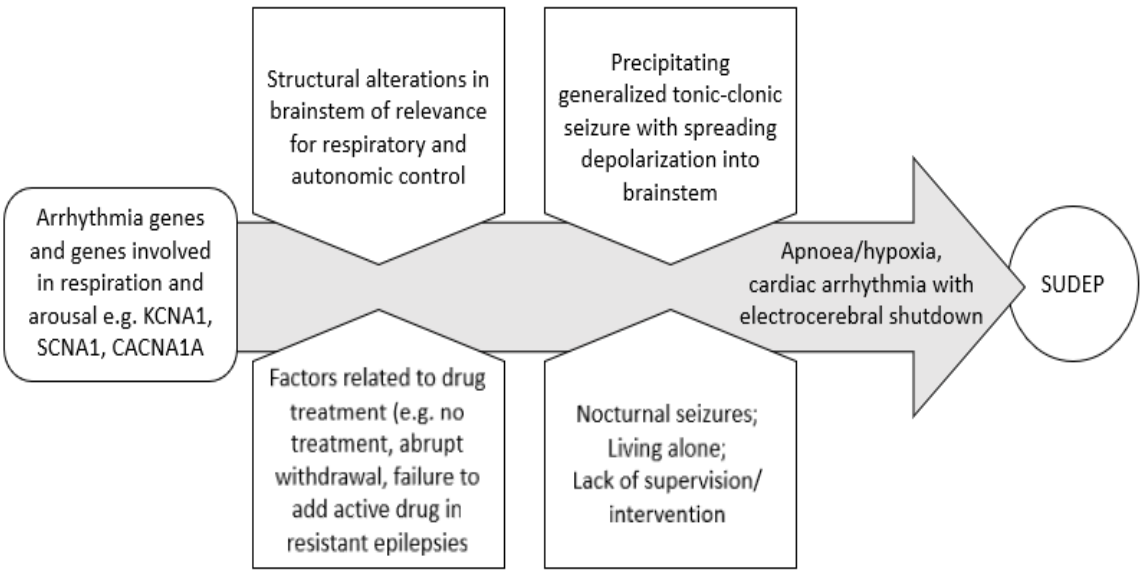

Figure 3. Showing the hypothetical predisposing and precipitating factors leading to SUDEP

The MORTEMUS study (Ryvlin et al., 2013) analyzed 11 SUDEPs that had occurred during video-EEG monitoring. All 11 had terminal GTCS. Commonly the victims had had several GTCS in the days leading up to the death. A consistent pattern was present in all patients where cardiorespiratory data were available for analysis. There was an initial postictal tachypnoea, often with sinus tachycardia, followed by bradycardia or bigeminy, or irregular heart rhythm in all cases. Within three minutes after this, all patients suffered from transient or terminal cardiorespiratory dysfunction (i.e., apnoea and bradycardia), and then followed shortly afterwards by asystole. In summary, all died from a combination of apnea, bradycardia (not tachyarrhythmias) and an arousal failure. Furthermore, all SUDEP cases in the MORTEMUS study occurred at night. A postictal generalized EEG suppression (PGES) was observed in all SUDEP victims in the MORTEMUS study (Ryvlin et al., 2013). Arousal impairment, autonomic dysregulation and greater respiratory dysfunction are seen more frequently in patients with PGES (Devinsky et al., 2016a) but it is not observed after all GTCS, even in the same patient and the association between PGES and SUDEP is debated (Surges et al., 2011).

One hypothetical model proposed for the mechanism of SUDEP (Massey et al., 2014) is based on the assumption that seizures activate neurons that project to the midbrain and medulla which in turn causes dysfunction of both the ascending arousal system and descending arousal system. With the seizure spreading to the midbrain it causes dysfunction of the ascending arousal system, including serotonergic neurons and this inhibition can then cause unresponsiveness and PGES postictally. Seizure spreading to the medulla may cause dysfunction of the descending arousal system, including the component that descends to the respiratory network in the medulla (Ryvlin et al., 2019). This, along with increased extracellular adenosine, may impair respiratory, cardiovascular and other autonomic control

neurons, while cortical activity is suppressed with PGES. Hypoventilation is then followed by post-ictal hypercapnia and hypoxia which can lead to bradycardia, asystole and death.

The hypotheses discussed above assume a key role of the brain stem in SUDEP and recent studies have found brain stem abnormalities in SUDEP victims. In one study where MRIs were reviewed retrospectively, SUDEP victims had widespread brainstem volume loss evident before death (Mueller et al., 2018) and that volume loss in brainstem regions (periaqueductal grey/medulla oblongata) correlated with reduced heart rate variability. In a neuropathological postmortem analysis of 40 cases (14 SUDEP, 6 epilepsy controls, 13 non-epilepsy controls) there were significant alterations in ventrolateral medulla in SUDEP cases with greater reduction in serotoninergic and galaninergic systems i.e. medullary respiratory neuronal groups (Patodia et al., 2018).

In animal models of epilepsy, respiratory depression has been demonstrated as an early postictal event leading to SUDEP (Li and Buchanan, 2019). In one animal model, pre-treatment with the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine, could prevent postictal respiratory arrest (Tupal and Faingold, 2006). In human subjects with epilepsy, preliminary data indicates that selective serotonin reuptake inhibitors can reduce post ictal desaturation, interestingly in focal seizures but not focal to bilateral tonic-clonic seizures (Bateman et al., 2010).

2.5.3 Genetic factors and SUDEP

Genetic factors can also play a certain role and may potentially help identify patients at risk of SUDEP. In one study of 61 SUDEP patients, clinically relevant mutations were found in a substantial amount of cases; In 22% there were cardiac arrhythmia genes and in one fourth of

the cases there were epilepsy genes (Bagnall et al., 2016). The genes involved are often so-called brain-heart genes which can both contribute to the cause of the epilepsy and make the individual more vulnerable to arrythmias and sudden death. Animal models have found at least nine different brain-heart genes that may contribute to a genetic susceptibility for SUDEP (Glasscock, 2014). Many of these gene defects are located in ion channel genes or genes modulating ion channel function that predispose humans and/or animal models to both seizures and fatal cardiac arrhythmias or in genetic defects in the serotonergic or autonomic systems (Dlouhy et al., 2016).

2.5.4 Incidence of SUDEP

Due to methodological limitations in previous studies, estimates of the incidence of SUDEP are somewhat uncertain (Devinsky et al., 2016a). In a recently published Practice guideline summary based on a systematic review and meta-analysis carried out by the American Academy of Neurology (AAN) and the American Epilepsy Society (AES) (Harden et al., 2017) the authors found the current evidence level with respect to the incidence of SUDEP to be low to moderate. Unfortunately, SUDEP does not yet have an International Classification of Disease code which hampers registration and research on SUDEP. Furthermore, SUDEP is both underreported and under recognized by clinicians who complete death certificates and also by medical examiners (Schraeder et al., 2009).

A systematic review and pooled analysis of high-quality population studies estimated the crude annual incidence of SUDEP to be 1.16 (0.95-1.36) per 1,000 persons with epilepsy (Thurman et al., 2014). Estimates were based on three population-based studies where SUDEP cases were ascertained through the Medical Examiner, Coroner, or hospital post-mortem registers in the US or UK, and the SUDEP incidence was calculated based on a

presumed prevalence of epilepsy in the catchment area (Leestma et al., 1989; Langan et al., 1998; Opeskin and Berkovic, 2003). However, the risk of SUDEP varies greately within the epilepsy population (Tomson et al., 2008). In fact, reported SUDEP incidence ranges from to 0.09 per 1000 person-years in newly diagnosed patients in population-based studies up to 9 per 1000 person-years in treatment resistant patients (Tomson et al., 2008; Devinsky et al., 2016a). Hence, there is a 100-fold range in SUDEP incidence within the epilepsy population (Téllez-Zenteno et al., 2005; Tomson et al., 2008). Previous studies have indicated greater risk among males (Hesdorffer et al., 2011) and at ages between 20-40 years (Holst et al., 2013, Thurman et al., 2014), whereas SUDEP has been considered rarer in children (Donner et al., 2001; Weber et al., 2005; Berg et al., 2013; Harden et al., 2017) and older age groups (although rarely assessed).

2.5.5 Circumstances surrounding death in SUDEP

SUDEP is in most cases unwitnessed and occurs most often during sleeping hours (Lamberts et al 2012) where victims are often found dead in bed (Kloster and Engelskjon, 1999; Opeskin and Berkovic, 2003). When occurring during sleeping hours, SUDEP was four times more likely to be unwitnessed than during awake hours (Lamberts et al., 2012). It thus seems that SUDEP frequently occurs when patients are unattended or without supervision. Early support for this notion came from a study of children with epilepsy in residential care (Nashef et al., 1995). In this group, all SUDEPs occurred while the children were on leave from the institution and did not have their regular supervision (Nashef et al., 1995). This is also in line with a case-control study (Langan et al., 2005) which indicated a protective role for a listening devise or regular checks during the night or sharing a bedroom with someone capable of giving assistance. Likewise, another study reported SUDEP to be more common in an epilepsy center with less supervision at night compared to another comparable epilepsy center with more supervision at night (van der Lende et al., 2018). In the previously cited

review from the AAN/AES (Harden et al., 2017) the authors considered lack of nocturnal supervision, and absence of nocturnal listening device to be risk factors with moderate confidence. SUDEP victims are often found in the prone position. In one study, which combined information from several studies, where body position was documented, 73% of 253 SUDEP victims were found in a prone position (Liebenthal et al., 2015). In the MORTEMUS study, the victim usually turned to a prone position during the seizure (Ryvlin et al., 2013).

2.5.6 Risk factors in SUDEP

With SUDEP being the major epilepsy related cause of death in people with epilepsy (Thurman et al., 2014; Thurman et al., 2017), the search for SUDEP risk factors has been intense over the past three decades. This has been done mainly in retrospective case-control studies where clinical characteristics have been compared between SUDEP victims and living people with epilepsy or non-SUDEP deaths. These studies vary considerably in risk factors analyzed, study population size, selection of controls and in generalizability. The most common approach has been to use living epilepsy controls to identify epilepsy patients at risk, i.e. what separates living epilepsy patients from those who have died from SUDEP. An overview of such studies is presented in Table 1.

Table 1. Case-control studies evaluating risk factors associated with SUDEP

Studies (year, country)	Study population	Cases/controls; N	Increased risks
Nilsson (1999, 2001) Sweden	Hospital discharge register	57/171	More than 2 seizures/year Polytherapy with AEDs Onset of epilepsy under 15 years Changes of AED dose Use of antipsychotic drugs
Langan (2005) UK	Multiple sources	154/616	Frequent GTCS History of GTCS Many AEDs ever used Current use of carbamazepine Supervision or special precautions at night protective
Hitiris (2007) Scotland	Epilepsy center	62/124	Seizure during last year. Onset of epilepsy before 15 years
Surges (2010) UK	Epilepsy center adults with pharmacoresistant focal epilepsies	19/19	Frequent GTCS
Aurlien (2007) Norway	Multiple sources	19/63	Females on lamotrigine
Walczak (2001) USA	Epilepsy centers	20/80	GTCS Polytherapy Onset of epilepsy <15 years Epilepsy duration >30 years Mental retardation

Most studies have been relatively small with well below 100 cases in each, except one study from the UK (table 1.) (Langan et al., 2005). There have also been studies using controls with epilepsy that have died from non-SUDEP causes, which can be used to shed light on the circumstances surrounding the death more than to identify risk factors (Kloster and Engelskjon, 1999; Opeskin and Berkovic, 2003; Tomson et al., 2008).

The majority of case-control studies have shown frequent GTCS (focal to bilateral or generalized tonic-clonic seizures) to be a significant risk factor (Nilsson et al., 1999; McKee and Bodfish, 2000; Walczak et al., 2001; Langan et al., 2005; Hitiris et al., 2007). In one study, the risk of SUDEP was 23 times higher in those who had experienced any seizure during the year of observation compared with seizure free patients (Nilsson et al., 1999) and all three case-control studies that allowed for quantifying the risk by different levels of

seizures found that the risk increased with the frequency of GTCS (Walczak et al., 2001, Langan et al., 2005). When data from four of the case-control studies, with living epilepsy controls, cited above (Nilsson et al., 1999; Walczak et al., 2001; Langan et al., 2005; Hitiris et al., 2007) were pooled (Hesdorffer et al., 2011) the following were identified as risk factors for SUDEP: male sex (OR 1.42), epilepsy onset before age 16 years (OR 1.72), disease duration of more than 15 years (OR 1.95), and number of GTCS per year (OR 5.07 for one to two GTCS per year and OR 15.46 for three or more of these seizures per year). In the more recent systematic review from the AAN/AES (Harden et al., 2017) GTCS was identified as the major risk factor (high confidence) and SUDEP risk increased with increasing frequency of GTCS (moderate confidence). Alcohol abuse has also been associated with SUDEP (Hesdorffer et al., 2011; Harden et al., 2017). The AAN/AES found low evidence that the following risk factors were associated with SUDEP risk: nocturnal seizures, lamotrigine use in women, never been treated with an AED, number of AEDs used overall, extratemporal epilepsy, intellectual disability, male sex, anxiolytic drug use, any specific AED, heart rate variability (Harden et al., 2017). Furthermore, the AAN/AES guidelines found other 17 previously suggested risk factors to have very low or conflicting evidence regarding SUDEP risk.

2.5.7 Antiepileptic drug treatment, adherence and SUDEP risk

Risk factors related to drug treatment are among the most important since these are amenable to changes and thus represent opportunities for prevention of SUDEP. A key question is whether AED treatment also affects the risk of SUDEP. As SUDEP is related to seizure occurrence, it is reasonable to assume that an effective drug treatment would reduce the incidence of SUDEP. Excess risk of SUDEP has been observed in relation to polytherapy (Nilsson et al., 1999; McKee and Bodfish, 2000; Walczak et al., 2001), but in a pooled

analysis of data from four studies, AED polytherapy was not associated with increased risk of SUDEP after adjustment for GTCS frequency (Hesdorffer et al., 2012). These findings are supported by those of a meta-analysis of 112 randomized controlled trials of adjunctive AED treatment for refractory focal seizures, including 18 definite or probable SUDEPs; The risk of SUDEP was much lower, OR 0.17 (95 % CI, 0.05–0.57), among those randomized to effective add-on AED treatment compared to add-on placebo (Ryvlin et al., 2011). Additionally, in the video-EEG monitoring study (MORTEMUS), SUDEP occurred after tapering AED treatment by at least 50% in all 10 cases where such information was available (Ryvlin et al., 2013). Taken together these data suggest that no treatment and/or tapering treatment is a risk factor. The systematic review stated that not adding an AED when patients are medically refractory was a risk factor with moderate confidence level (Harden et al., 2017).

Carbamazepine treatment (Timmings, 1993, Langan et al., 2005) and high plasma concentrations of carbamazepine (Nilsson et al., 2001) were associated with a slight increase in risk for SUDEP. This is not implausible since carbamazepine can reduce heart-rate variability (Persson et al., 2003), which has been a predictor of increased sudden death in other conditions. A small case-series suggested an association between use of lamotrigine in women with idiopathic epilepsy and SUDEP (Aurlien et al., 2007). It should be emphasised, however, that observations on SUDEP risk with these two AEDs have not been confirmed in other studies such as the pooled analysis of four case-control studies, when adjustment was made for seizure frequency (Hesdorffer et al., 2012) and a meta-analysis of 42 randomised controlled studies of lamotrigine found no increase (Tomson et al., 2013).

Poor adherence to AEDs has been suggested as a risk factor for SUDEP (Téllez-Zenteno et al., 2005; Tomson et al., 2005; Monté et al., 2007). Data are, however, so far non-conclusive due to methodological limitations of previous studies. In a retrospective cohort study, Faught and colleagues (Faught et al., 2008) used Medicaid claims data to evaluate adherence to treatment in more than 33,000 patients with AED prescriptions. Non-adherence was associated with a more than threefold increase in mortality compared to adherence. A similar result was observed in a large study from the UK (Risdale et al., 2011). Unfortunately, both these investigators analysed all causes of mortality and not SUDEP specifically. In summary, SUDEP in relation to adherence has not been specifically studied.

The systematic review (Harden et al., 2017) concluded that the evidence is low for any specific AED, or for lamotrigine use in women to be associated with increased SUDEP risk, and very low or conflicting for a difference between monotherapy vs. polytherapy or for psychotropic drug use. The practice guideline summary stressed the importance of therapy adherence to maintain freedom from GTCS, although non-adherence as a SUDEP risk factor has not been assessed appropriately.

2.5.8 Other drug treatment and SUDEP risk

It is conceivable that drugs other than AEDs could affect SUDEP risk. Based on data from an epilepsy mouse model, it has been suggested that treatment with antidepressants of the SSRI type, could reduce the SUDEP risk (Tupal and Faingold 2006). The proposed mechanism is by prevention of postictal respiratory arrest. Pharmacological treatment, with drugs such as beta blockers has been used successfully in prevention of sudden cardiac death in patients at high risk for reasons such as ischemic heart disease, congestive heart failure and post myocardial infarction (Arshad et al., 2008). Although a different population, it is reasonable

to consider the possibility of a preventive effect of drugs such as beta blockers and statins on SUDEP in epilepsy patients, given the similarities of the final event. However, the effects in prevention of SUDEP with SSRIs, beta blockers or statins have never been assessed. It is very unlikely that these drugs will be analysed in randomized controlled trials unless epidemiological data supports their effectiveness.

2.5.9 Vagus nerve stimulation, epilepsy surgery and SUDEP

It is unclear if vagus nerve stimulation reduces the risk for SUDEP. One study (Annegers et al., 2000) showed a lower than expected rate of SUDEP in a cohort of treatment resistant epilepsy patients treated with vagus nerve stimulation while another study did not (Granbichler et al., 2015). Since seizure control is the most likely approach to reduce the risk of SUDEP, successful epilepsy surgery may also reduce the risk of SUDEP. In a large follow up study of 583 surgical patients, SUDEP was significantly associated with seizure control ($p=0.001$) (Sperling et al., 2005). In 18 of 19 SUDEP deaths, patients were not seizure free. In another study that included 305 patients who underwent temporal lobe epilepsy surgery over a 20-year period, SUDEP rates were lower than those reported for similar patient populations with chronic epilepsy (Hennessy et al., 1999).

2.6 SUMMARY AND CONCLUDING REMARKS ON THE CURRENT STATE OF KNOWLEDGE

Although SUDEP has attracted increasing attention from the scientific community during the last 20 years, important gaps in knowledge still exist that hamper the development of methods aiming at prevention of this, the most devastating consequence of epilepsy. We are still missing large population-based studies on the incidence of SUDEP, which is important both in order to understand whom to target with preventive measures and how to assess

effectiveness of interventions. Our understanding of the circumstances surrounding SUDEP is incomplete which is a major limitation when it comes to development of seizure monitoring and potential SUDEP-preventing devices. Finally, our understanding of risk factors for SUDEP is limited to a few established risk factors. There is only one risk factor with high confidence level, five with moderate and 17 with low or very low as assessed in the recent systematic review (Harden et al., 2017). The low confidence level is often due to methodological issues. In particular, more data are needed to understand the potential role of pharmacological treatment for SUDEP prevention.

3 AIMS

3.1 General aims

The objective of the thesis was to provide new information on the incidence, circumstances, and risk factors of SUDEP, with the overall aim of providing a basis for the development of future actions to prevent this devastating consequence of epilepsy.

3.1.1 Specific aims

The specific aims were to study:

1. The age and sex specific incidence of SUDEP in the Swedish population (paper I).
2. The circumstances surrounding SUDEP such as living conditions, if death was witnessed, place, time and body position at death (paper II).
3. The influence of clinical factors including GTCS, nocturnal seizures and comorbid diseases on the risk of SUDEP (paper III).
4. The risk of SUDEP in relation to AED treatment, including mono vs. polytherapy, adherence and treatment with SSRIs, statins, beta-blockers and antipsychotic drugs (paper IV).

4 SUBJECTS AND METHODS

4.1 Subjects

4.1.1 Overview of study population

The project is based on a study population (n=78 524) which comprises all persons living in Sweden at 1. July 2006, who at some point during 1998-2005 where registered with the diagnosis code for epilepsy (ICD G 40) in the Swedish National Patient Register (SNPR). The SNPR contains all patients hospitalized (with total national coverage from 1987) or managed in hospital-based ambulatory care (since 2001) in Sweden. Although not yet formally validated for epilepsy, the register has been validated for several diagnoses, and shown a high accuracy (Ludvigsson et al., 2011). Each individual's outpatient visit or hospital discharge diagnosis (ICD code) is linked with their unique personal identification number.

4.1.2 SUDEP case ascertainment

To identify cases of SUDEP, the study population was linked to the National Cause-of-Death Register. During the follow-up time from July 1, 2006 to December 31, 2011, we identified 9605 deaths. All death certificates in the study population between 1 July 2006 and 31 December 2011 with epilepsy mentioned on death certificate and all deaths during 2008 (n=3166) were reviewed by Olafur Sveinsson (figure 4). Based on the information in the death certificates, obvious non-SUDEP deaths were excluded from further analysis. For all others we analyzed patient medical records, autopsy and police reports (Olafur Sveinsson) and information was extracted using a standardized protocol. Those who did not have epilepsy and obvious non-SUDEP cases were excluded. Two neurologists (Olafur Sveinsson and Torbjörn Tomson) reviewed the remaining potential SUDEP cases and classification was

made through consensus. When needed, a forensic pathologist was consulted. By using this methodology, 329 SUDEP cases were collected.

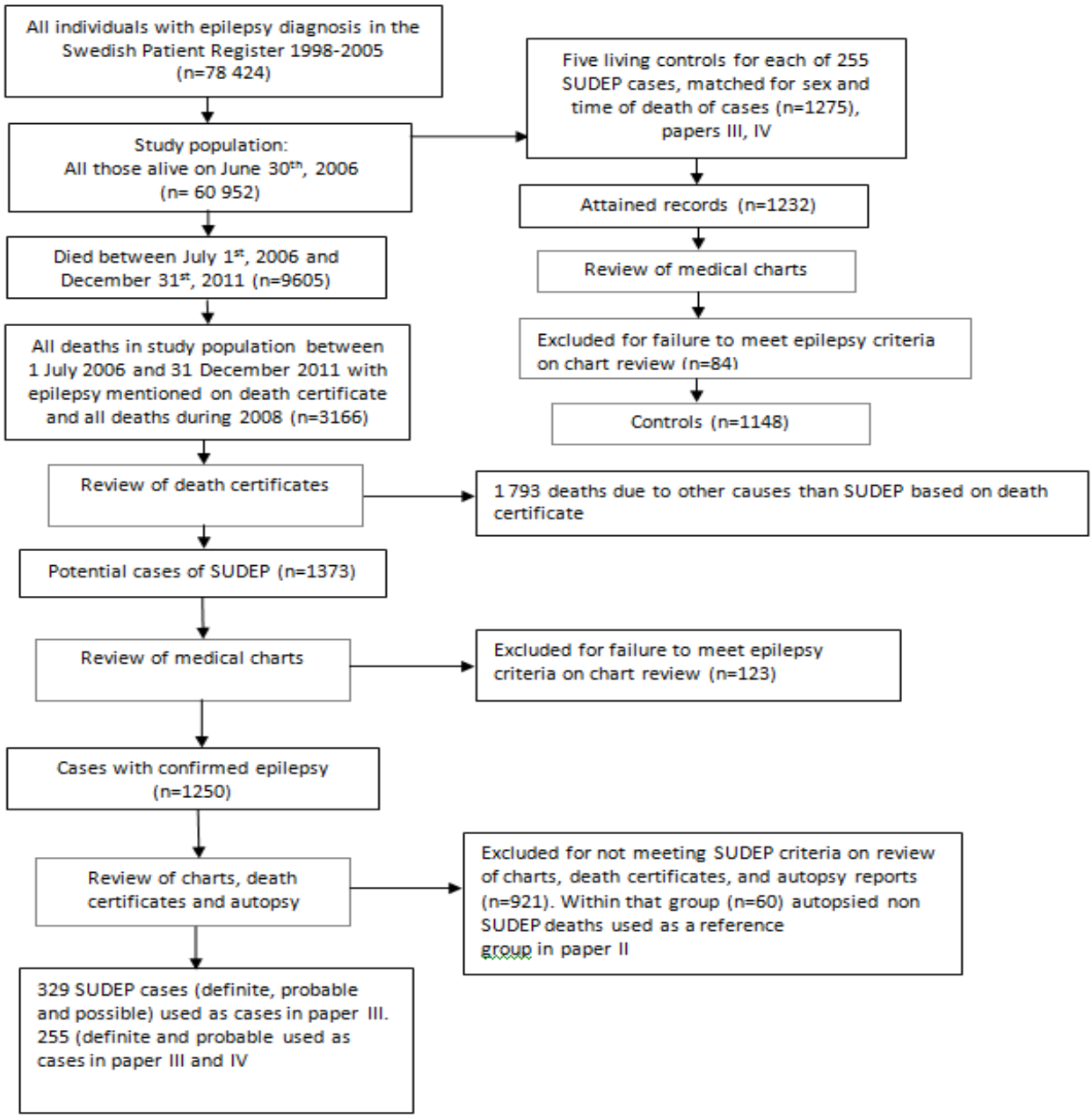

Figure 4. Flow chart over case and control selection in papers II-IV

4.1.3 Selection of controls

From the study population, five epilepsy controls (n=1275) per SUDEP case, of the same sex, who were alive at the case´s time of death, were randomly selected by the National Board of Health and Welfare. The index date for the controls was time of death for the matched case. Medical records were attained for 97% (n=1232) of the controls. After case review, 6.8% (n=84) of them were judged not to have epilepsy. This left 1148 individuals who served as controls (figure 4).

4.2 METHODS

4.2.1 The incidence of SUDEP (paper I)

The SUDEP incidence study was based on an in-depth assessment of all deaths for one year, 2008. All individuals with a hospital-based ambulatory care or hospital discharge diagnosis of epilepsy in the Swedish National Patient Registry during 1998-2005 who were alive on January 1st, 2008 (n=57 775) were included. We identified deaths during 2008 by linkage to the National Cause-of-Death Registry. Death certificates for all who died during 2008 (n= 1891) were retrieved. Obvious non-SUDEP were excluded and information collected on potential cases as described above. Two neurologists (Olafur Sveinsson and Torbjörn Tomson) classified the SUDEP cases (n=99) according to two different proposals, the Annegers' criteria (Annegers, 1997) and the unified definition of SUDEP proposed by Nashef et al (Nashef et al., 2012), respectively. The SNPR was used to identify those in the epilepsy study population that had psychiatric comorbidity registered during 1998-2005 (ICD 10 code F 00-99).

4.2.2 Circumstances of SUDEP (paper II)

Information from all 329 SUDEP (definite, probable, and possible according to Annegers' criteria) cases identified 2006 to 2011, regarding circumstances was extracted from patient, autopsy and police records. The following information was extracted: living conditions (living alone, with others, sharing a bedroom), body position (prone, supine, sitting, lateral, on the side or unknown) when found dead, witnessed or not (individuals observed from a healthy state until dead were considered witnessed), seizure in conjunction with death, or indirect signs indicating seizure, time of day, time of week, time of year, location (at home and where, outside of home or in hospital). Time of death was classified as: Daytime (08.00-16.00), Evening (16.00-00.00) or Nighttime (00.00-08.00). In seventeen cases, the day but not time of death could be determined. Death during June, July and August was categorized as occurring during summertime. Death during all other months was classified as other. Weekends and public holidays were considered as non-working days while all other were working days.

Autopsied non-SUDEP group

Since living epilepsy controls cannot be used as controls when it comes to the circumstance of death we used 60 cases with an initial suspicion of SUDEP, but for which autopsy records revealed another definite cause of death with the following being the most common causes; mycocardial infarction (21), heart failure (8), traumatic brain injury (7), pneumonia (6), status epilepticus (5). These autopsied non-SUDEP cases provided a reference group for our 167 definite SUDEP cases, who also had undergone an autopsy.

4.2.3 Clinical risk factors in SUDEP (paper III) and pharmacological treatment and SUDEP risk (paper IV)

Of the 329 SUDEP cases described above, only definite (n=167) and probable (n=88) but not possible SUDEP cases (n=73) were used for case-control analyses. For all cases and controls, we used patient records to collect information as described in paper II above and additionally on type of epilepsy, etiology (Scheffer et al., 2017), epilepsy onset, duration of epilepsy, history of GTCS (including both generalized tonic-clonic seizures and focal to bilateral tonic-clonic seizures) (Fisher et al., 2017), presence and frequency of nocturnal GTCS during last year of observation, presence of other seizures during the last year of observation, history of nocturnal seizures, history of nocturnal GTCS, presence of nocturnal GTCS during last year of observation, intellectual disability, AEDs and whether the patient had undergone epilepsy surgery or had ongoing treatment with vagus nerve stimulation (VNS).

By means of ICD codes from the SNPR we obtained information on pulmonary, cardiovascular and psychiatric comorbidity (from 1997 to death or index date). Information on highest educational level was attained from the Longitudinal integration database for health insurance and labor market studies (LISA), which holds annual registers since 1990 and includes all individuals 16-74 years of age. In the LISA register, this information is recorded as missing for individuals below 16 years and for those who did not attend regular school due to intellectual disability.

Information from Swedish Prescribed Drug Register

The National Prescribed Drug Register records information on all prescribed drugs dispensed at Swedish Pharmacies since July 2005. Medications are classified according to Anatomical Therapeutic Chemical (ATC) classification system and in the present study, ATC code N03A was used for AEDs. For the current analysis we focused on the seven most frequently used

AEDs among our cases and controls. Using data from this register we classified AED usage in the following way; Taking an AED: AED dispensed within 90 days of death or index date, since in Sweden, drug dispensing cannot be for longer than 90 days at a time; Not taking an AED: no AED dispensed within 360 days of death or index date; Undetermined group: AED dispensed between 90-360 days but not within 90 days from death or index date.

Monotherapy: only one AED dispensed within 90 days of death or index date: Polytherapy: two or more AEDs dispensed within 90 days of death or index date; We also collected information on concomitant treatment with neuroleptics (ATC N05A), antidepressants (ATC N06A), beta blockers (ATC C07A) and statins (ATC C10A). Cases and controls were considered to use the above-mentioned medications if they had been dispensed within 90 days of death or index date.

4.3 Statistical analysis

For all papers, the final statistical analysis was performed with SAS software (SAS software, Version [9.4] of the SAS System for [MS Windows], SAS Institute Inc.).

Paper I

Incidence rates of SUDEP were estimated together with exact 95 % confidence intervals (CIs) (Garwood, 1936). We also calculated incidence rate ratios in relation to sex and psychiatric comorbidities, together with 95% exact confidence intervals (Sahai 1996).

Paper II

P-values for comparisons between SUDEP cases and non-autopsied controls were calculated from the two-sided t distribution for means and with the chi-squared distribution for proportions and incidences. Incidence was calculated as number of SUDEP cases per calendar month, weekday and working days and non-working days respectively, divided by the number of person years.

Papers III-IV

In papers III and IV the association between SUDEP and potential risk factors were estimated by ORs with 95% CIs calculated by conditional logistic regression to account for matching by sex and calendar time. As the control participants were sampled with an incidence density method, the ORs can be interpreted as incidence rate ratios (Vandenbroucke and Pearce, 2012). In paper III, ORs were adjusted for age and sex (model 1), age, sex and GTCS frequency (model 2) and age, sex, GTCS frequency and nocturnal GTCS last year of observation (except in the analyses of seizures), living conditions and AEDs (model 3). In paper IV, ORs were adjusted for age and sex (model 1), age, sex, duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, education level (model 2). Model 3 is adjusted for the same variables as model 2 together with history of GTCS, GTCS frequency last year of observation and nocturnal GTCS last year of observation. In the thesis, results of model 3 are discussed unless otherwise stated. We used proportion attributable to interaction (AP) (Andersson et al., 2005) in paper III to assess interaction between GTCS during last year of observation (yes/no) and sharing a bedroom (yes/no), defined as departure from additivity of effects. The formula for AP is: $(OR_{11} – OR_{10} – OR_{01} + 1) / OR_{11}$, where OR_{11} indicates doubly exposed (having GTCS and sleeping alone) and OR_{01} or OR_{10} indicate either one exposure (sleeping alone or

having GTCS). The reference group is those with neither exposure, and the ORs were adjusted for age and sex (matching variable).

4.4 Ethical considerations

Our study design relies on access to personal data from different registries, individual medical records and for potential cases also from autopsy and police reports, and without obtaining individual informed consent from relatives (for cases) or directly from patients (for controls). Apart from the methodological issues with in particular risk of substantial loss of cases and controls and thus representativeness, we considered that approaching relatives and in particular patients to obtain informed consent may cause harm. Surveys among neurologists have shown that most do not inform their epilepsy patients about SUDEP (Morton et al., 2006). An information letter on SUDEP from the research group to the patients, whether through their physician or not, could pose anxiety and unreasonable concern for future health risks. For these reasons we concluded that attempts to obtain informed consent would cause more harm than benefit for the patients involved. To avoid ordering patient records and information for more controls than necessary, we first identified the cases. After extracting information from medical records and registers for both cases and controls, all individuals were deidentified and data kept anonymized. The Ethics Committee of Karolinska Institutet approved the study and granted that individual informed consent was not required.

5 MAIN RESULTS

5.1 The incidence of SUDEP (paper I)

During 2008, 1890 individuals from the study population died. Of these, 99 met Annegers' SUDEP criteria (49 definite, 19 probable, and 31 possible). Definite and probable SUDEP accounted for 3.6% of all deaths in the study population during the year 2008, and 5.2% when possible was included. In the age group 0-15 years, the relative contribution of SUDEP (definite, probable and possible) to overall deaths was 36.0% (9/25), 21.3% (34/160) between 16-50 years and 3.3% (56/1706) above 50 years. SUDEP incidence was 1.20/1000 person-years (definite/ probable according to Annegers' definition), 1.24/1000, (definite/probable/SUDEP-plus according to Nashef's definition) and 1.74/1000 if possible SUDEP was included according to the former definition. Although with overlapping confidence intervals, the trend was for higher incidence of definite/probable SUDEP among those above 50 years (figure 5) and the proportion of possible cases increased with age (figure 6). Incidence was higher in males (1.41/1000), than in females (0.96/1000), but only when possible SUDEP was included. Notably, there was no SUDEP case among girls <16 years but seven boys. The incidence was higher among those with psychiatric comorbidities compared to those without, particularly among females, rate ratio 5.15, 95% CI: 2.17-13.10.

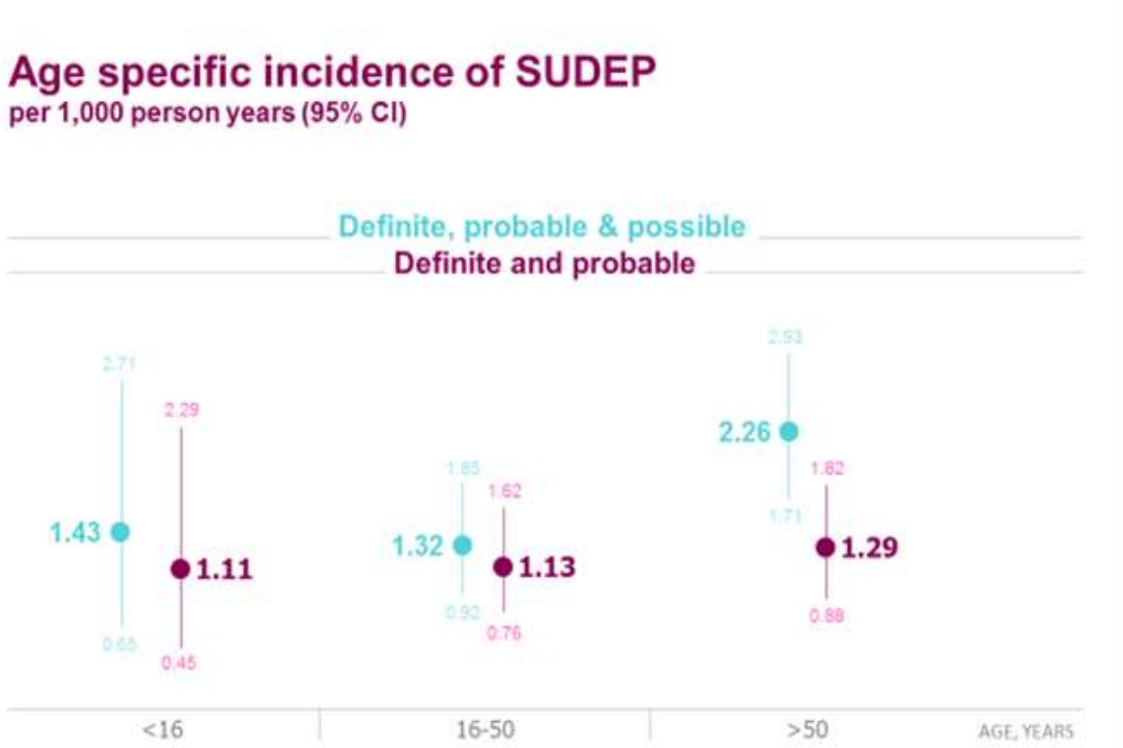

Figure 5. Incidence of SUDEP over different ages both for definite and probable and definite, probable and possible

Out of the 99 cases with definite, probable, or possible, SUDEP was listed as the immediate cause of death on the death certificate in one case only: In 27 out of 99 cases either SUDEP, seizures, or epilepsy was indicated as the immediate cause of death. Epilepsy was mentioned in any position of the death certificate in 63.6% of the 99 SUDEP cases and in 15.2% of the 1890 individuals with an epilepsy diagnosis who died during 2008.

5.2 Circumstances of SUDEP (paper II)

Of the 329 SUDEP deaths (definite (n=167), probable (n=89) possible (n=73), more than half (58%) occurred at night and 91% died at home, whereof 65% were found deceased in bed (figure 6). Death was witnessed in 17% of all SUDEP cases. When a seizure was witnessed in conjunction with SUDEP (n=49) all were GTCS. In four witnessed cases no seizure was

observed and in three cases this was uncertain. In two thirds of cases (67%) there was either a witnessed seizure (15%) or indirect indications of a seizures (52%).

If SUDEP occurred during the night (58%) compared to during the day or evening (37%), it was more likely not to be witnessed (p=0.013). In the SUDEP cases where body position was documented (43%), more than two thirds (70%) were found prone (figure 6). Dying at night made it more likely (80%) to be found prone than other times (55%) (p<0.001). Among adult SUDEP cases, 75% were living alone, and only 14% of all SUDEP cases shared a bedroom (figure 6). We found a non-significant indication for higher incidence during the summer months compared with the rest of the year; 0.96 vs. 0.79 per 1000-person years (p=0.86) and on non-working days, compared with working days, 0.94 vs. 0.79 per 1,000-person years (p=0.19).

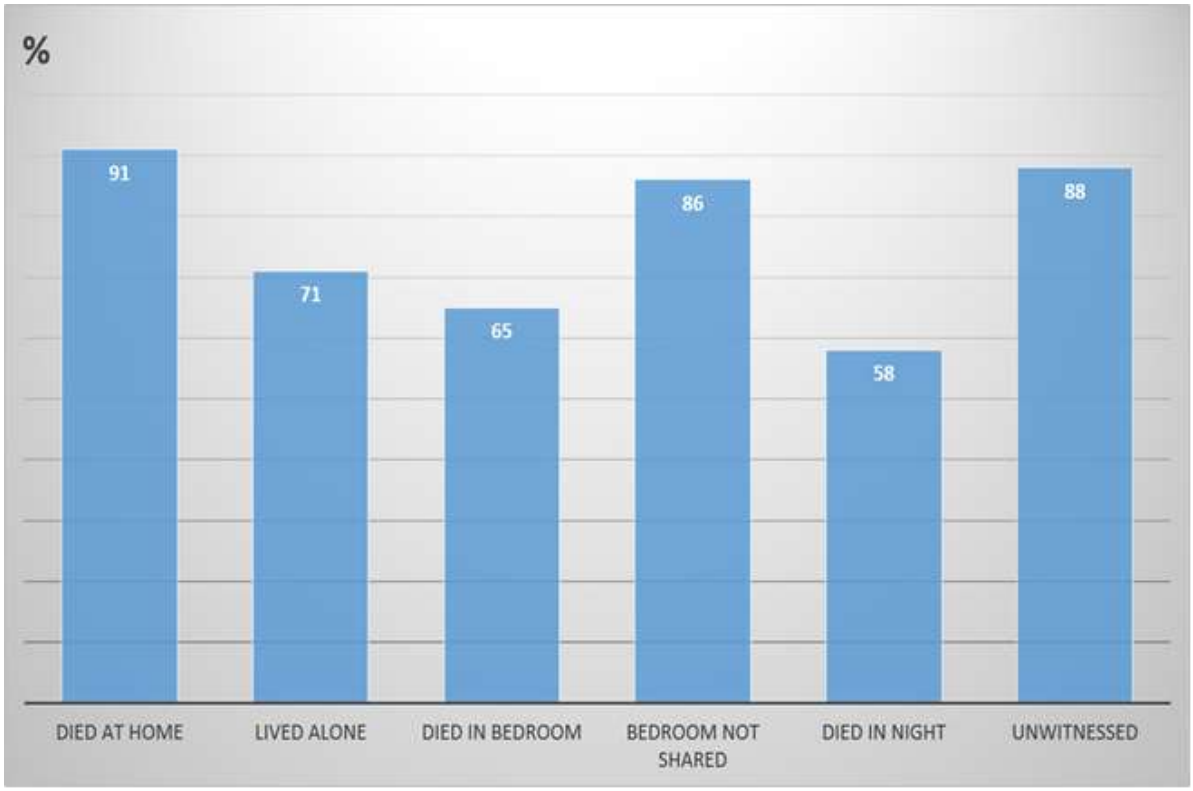

Figure 6. Circumstances at death in 329 SUDEP cases; proportion (%) of cases

In comparison to the the autopsied non-SUDEP group, the definite SUDEP patients died more often unwitnessed, with a preceding seizure, at home, in bed during the night, were more often found in the prone position and to live alone (table 2).

Table 2. Differences between definite SUDEP cases (n=167) vs autopsied non SUDEP deaths (n=60) in relation to living conditions and circumstances surrounding death

	Definite SUDEP (n=167)	Autopsied non- SUDEP (n=60)	p value
Died during the night	59%	22%	p<0.001
Died at home	89%	43%	p<0.001
Witnessed	13%	67%	p<0.001
Seizure when witnessed	95%	21%	p<0.001
Prone position	82%	16%	p<0.001
Lived alone	65%	52%	p=0.014
Shared a bedroom	10%	45%	p<0.001

P value, comparison between definite SUDEP cases and non-SUDEP deaths with autopsy.

5.3 Clinical risk factors in SUDEP (paper III)

A clinical and demographic overview for the 255 SUDEP cases (167 definite, 88 probable) and 1148 controls included in analyses of paper III and IV can be seen in table 3. The cases had somewhat longer duration of epilepsy, more often focal epilepsy and of structural origin, and lived more often alone (68%) than controls (27%) (table 3).

Table 3. Demographic and clinical characteristics for cases and controls (papers III and IV)

	Cases	Controls
N (%)	255	1148
Mean age at death/index (range)	47 (4-92)	39 (3-94)
Mean age at epilepsy diagnosis (range)	22.4 (0-86)	20.0 (0-86)
Mean duration of epilepsy in years (range)	24 (1-81)	20 (1-78)
Type of epilepsy		
Generalized n (%)	37 (14.5)	267 (23.3)
Focal n (%)	186 (73.0)	794 (69.3)
Focal and generalized n (%)	10 (4.0)	31 (2.7)
Unknown n (%)	22 (8.6)	56 (4.9)
Causes of epilepsy		
Genetic n (%)	48 (18.8)	303 (26.4)
Structural	129 (50.6)	444 (38.7)
Infectious n (%)	12 (4.7)	42 (3.7)
Metabolic n (%)	2 (0.8)	9 (0.8)
Autoimmune n (%)	2 (0.8)	10 (0.9)
Unknown n (%)	66 (25.9)	359 (31.3)
Living conditions		
Sharing household and bedroom n (%)	32 (12.5)	391 (34.1)
Sharing household but not bedroom n (%)	49 (19.2)	398 (34.7)
Not sharing household n (%)	174 (68.2)	304 (26.5)
Unknown n (%)	0	55 (4.8)
Highest education		
Post-secondary education n (%)	26 (10.2)	168 (14.6)
High school/secondary education n (%)	86 (33.7)	359 (31.3)
Primary education n (%)	86 (33.7)	297 (25.8)
Missing education n (%)[a]	57 (22.4)	324 (28.2)

[a] Below 16 and those who did not attend regular school.

Those with a history of GTCS had a tenfold increased SUDEP risk and the risk was increased to 32-fold with 4-10 GTCS during the last year of observation (table 4). When a history of nocturnal GTCS was present, a nine-fold SUDEP risk was observed and a 15-fold risk was seen if nocturnal GTCS were present during the last year of observation (table 4). No increased risk of SUDEP was seen in those experiencing exclusively non-GTCS during the preceding year. There was a fivefold increased risk of SUDEP among those living alone, while the risk was reduced to twofold when sharing household but not bedroom. A 59% reduced SUDEP risk was associated with treatment with vagus nerve stimulation (table 4).

No association between level of education and SUDEP risk was observed. Individuals with a previous diagnosis of substance abuse or alcohol dependence had a twofold increased risk of SUDEP. Mental health disorders and intellectual disability, structural etiology, focal or focal and generalized epilepsy, longer duration of epilepsy and young age at epilepsy onset, were not associated with SUDEP, once we adjusted for frequency of GTCS. Albeit, epilepsy of unknown type remained associated with SUDEP.

Analyses of the combination of GTCS and living conditions indicated that compared to those without GTCS and who shared their bedroom with someone, individuals who experienced ≥4 GTCS during the last year of observation had 20 times increased risk if they shared their bedroom with someone, 34 times increased risk if they shared household but not bedroom and 82 times increased SUDEP risk if they lived alone. Interaction analysis indicated that individuals experiencing ≥1 GTCS and not sharing a bedroom with someone had 67-fold increased risk of SUDEP compared to individuals not having GTCS, who shared their bedroom with someone, with AP estimated at 0.69 (95% CI 0.53-0.85).

Table 4. Odds ratio (OR) and 95% confidence interval (CI) of SUDEP in relation to type and frequency of seizures and treatment

			Model 1[a]	Model 3[b]
	No. Cases	No. Controls	OR (95% CI)	OR (95% CI)
History of GTCS				
No	4	174	1	1
Yes	251	943	10.56 (3.86-28.86)	9.60 (3.44-26.82)
Seizures during preceding year				
No (ref)	26	577	1	1
Yes, but not GTCS	12	290	0.97 (0.48-1.96)	1.15 (0.54-2.46)
GTCS	217	280	22.70 (13.72-37.55)	26.81 (14.86-48.38)
0 (ref)	38	865	1	1
1-3	106	150	19.51 (11.94-31.88)	22.14 (12.74-38.46)
4-10	50	42	28.24 (15.36-51.92)	31.87 (15.95-63.67)
>10	61	88	26.38 (14.62-47.61)	29.70 (15.04-58.63)
No (ref)	63	711	1	1
Yes, non-GTCS	2	102	0.23 (0.06-0.98)	0.27 (0.06-1.15)
Yes, GTCS	190	335	8.44 (5.91-12.04)	9.04 (6.08-13.45)
No (ref)	145	1049	1	1
Yes	110	99	12.98 (8.61-19.56)	15.31 (9.57-24.47)
Epilepsy surgery				
No (ref)	242	1098	1	1
yes	13	50	1.27 (0.66-2.44)	0.77 (0.31-1.92)
VNS				
No (ref)	244	1098	1	1
yes	11	50	1.29 (0.65-2.57)	0.41 (0.17-0.98)
Living conditions				
Sharing household and bedroom (ref)	32	391	1	1
Sharing household but not bedroom	49	398	2.43 (1.36-4.32)	2.28 (1.14-4.58)
Not sharing household	174	359[e]	6.11 (4.04-9.22)	5.01 (2.93-8.57)

[a] Adjusted for age and sex (matching variable)
[b] Adjusted for age, sex, GTCS frequency and nocturnal GTCS last year of observation (except in the analyses of seizures), living conditions and AEDs

5.4 Pharmacological treatment and SUDEP risk (paper IV)

No AED, neither as monotherapy or in polytherapy combination increased the risk for SUDEP (figure 7). Using no AED treatment as reference, polytherapy, especially taking three or more AEDs was associated with a 69% reduced SUDEP risk after adjusting for GTCS

frequency and other covariates (table 5). Out of the seven most commonly used AEDs, only levetiracetam was associated with a significantly lower SUDEP risk when compared to no AED treatment (OR 0.10, 95% CI 0.03-0.61). Lamotrigine, valproic acid and levetiracetam were associated with a significantly reduced risk when used as part of a polytherapy (figure 7). SUDEP risk in relation to lamotrigine use was analyzed separately for females and there was no indication of excess risk neither when used as mono- nor polytherapy.

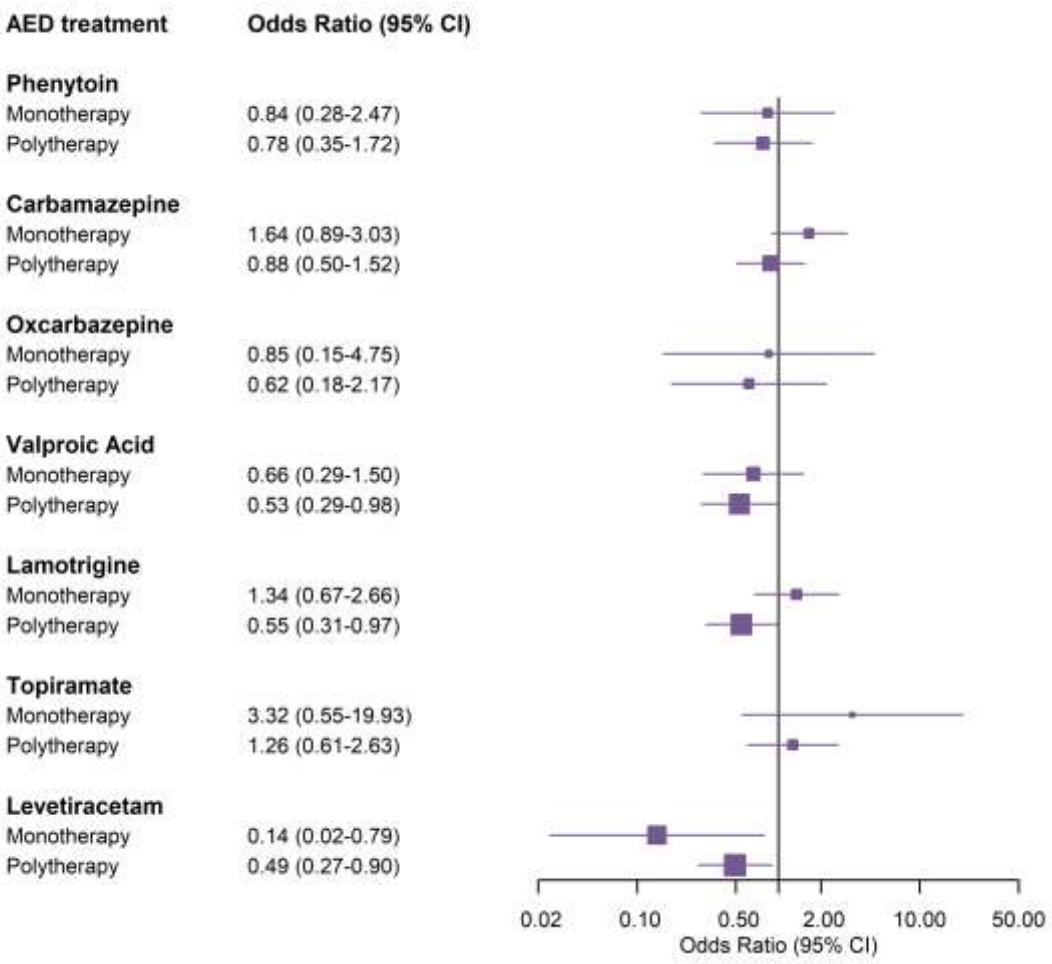

Figure 7. Forest plot showing odds ratio (OR) and 95% confidence interval (CI) of SUDEP in relation to specific antiepileptic drugs (AEDs) as mono and polytherapy (reference is individuals not on that AED, based on model 3).

When analyzing adherence, the analysis was restricted to individuals for which medical records stated that AEDs were prescribed during the last year of observation. Using 0-90 days as reference, individuals with 181-365 days since last dispensing had an OR of 2.96 (95% CI

0.46-18.86) when adjusting for GTCS among other covariates. While when not adjusting for GTCS in the same group, the risk became more pronounced and significant, OR 3.41 (95% CI 1.05-11.09). Similarly, having non-adherence mentioned in the medical record was associated with an OR of 2.75 (95% CI 1.58-4.78). Use of statins was associated with a reduced risk of SUDEP (OR 0.34, 95% CI 0.11-0.99) but we did not observe a reduced risk with SSRIs or other antidepressants, or beta blockers, nor an increased risk with neuroleptics.

Table 5. Odds ratio (OR) and 95% confidence interval (CI) of SUDEP in relation to anti-epileptic drugs (AED), time since last dispensed AED and non-adherence noted in medical records

	No. Cases	No. Controls	*Model 1*[d] OR (95% CI)	*Model 2*[e] OR (95% CI)	Model 3[f] OR (95% CI)
AED therapy					
No AEDs[a]	46	265	1	1	1
Monotherapy[b]	113	483	1.15 (0.79-1.69)	1.03 (0.67-1.57)	0.79 (0.44-1.41)
Polytherapy[c]	96	400	1.24 (0.83-1.84)	0.90 (0.57-1.42)	0.48 (0.26-0.90)
2 AEDS	65	272	1.22 (0.80-1.87)	0.94 (0.58-1.51)	0.59 (0.31-1.12)
≥3 AEDS	31	128	1.27 (0.76-2.12)	0.81 (0.45-1.48)	0.31 (0.14-0.67)
Time since last dispensed AED[h]					
0-90 days	199	871	1	1	1
91-180 days	16	85	0.85 (0.48-1.49)	1.13 (0.61-2.08)	1.20 (0.50-2.87)
181-365 days	6	15	1.99 (0.72-5.51)	3.41 (1.05-11.09)	2.96 (0.46-18.89)
>365 days	14	33	1.92 (0.99-3.71)	2.42 (1.14-5.14)	2.25 (0.73-6.90)
Non-adherence mentioned in medical record					
No	173	886	1	1	1
Yes	62	118	2.47 (1.73-3.54)	2.56 (1.70-3.84)	2.75 (1.58-4.78)

[a] No AED dispensed within 90 days of death or index date. [b] Only one AED dispensed within 90 days of death or index date. [c] Two or more AEDs dispensed within 90 days of death or index date. [d] Model 1 is adjusted for matching variables (sex and calendar time) and age. [e] Model 2 is adjusted for same variables as Model 1 together with duration and type of epilepsy, living conditions (sharing bedroom), intellectual disability, substance abuse, alcohol dependence, education level, [f] Model 3 is adjusted for same variables as Model 2 together with history of GTCS, GTCS frequency last year of observation and nocturnal GTCS last year of observation. [g] Seven most common monotherapies. [h] Restricted to individuals prescribed AEDs according to patient records.

6 DISCUSSION

6.1 MAIN FINDINGS

The purpose of this study was to examine the incidence, circumstances and risk factors for SUDEP in Sweden. Our results support the previous notion that SUDEP is a major cause of death in epilepsy patients, since our data suggest that approximately 100 patients die every year in Sweden due to SUDEP. Furthermore, SUDEP accounts for one third of deaths in children with epilepsy and one fifth of deaths among young adults with epilepsy. Since the majority died at home in bed, at night with indications of a previous GTCS, SUDEP can be considered as an event related to night time GTCS. We found no excess risk of SUDEP among individuals experiencing non-GTCS only, which has important clinical implications. GTCS and lack of supervision were the main risk factors. Compared to an epilepsy patient that shares bedroom and is free from GTCS, an individual with more than four GTCS a year who sleeps alone has an 82-fold increased SUDEP risk. Moreover, our results suggest that up to 69% of SUDEP cases could be prevented in individuals with GTCS who live alone, if they were made free from GTCS or did not sleep alone. An interesting finding was that polytherapy, in particular with three or more AEDs, was associated with a substantially reduced SUDEP risk, this notably after adjusting for GTCS. Regarding monotherapy, the lowest SUDEP risk was seen among users of levetiracetam and an increased SUDEP risk was observed among those considered to be non-adherent. Statins were associated with a reduced SUDEP risk whereas we found no support for a protective effect of SSRIs.

6.2 RESULTS IN RELATION TO PREVIOUS RESEARCH

6.2.1 The incidence of SUDEP

Despite some differences in methodology, our observed incidence of 1.20 (0.93-1.52) per 1000 person-years is very similar to the rate of 1.16 (0.95-1.36) reported in a pooled analysis (Thurman et al., 2014) of three high quality population-based studies (Leestma et al., 1989; Langan et al., 1998; Opeskin and Berkovic, 2003). However, our findings of incidence rates differ markedly from the incidence of 0.2-0.43 per 1000 that has been reported in children in the past (Donner et al., 2001; Weber et al., 2005; Hesdorffer et al., 2011; Berg et al., 2013; Thurman et al., 2014). Since then, a population-based study in Canada, has confirmed our findings on the incidence of SUDEP in children (Keller et al., 2018). Over a period of two years (2014-2015), the researchers found 17 pediatric SUDEP cases in the state of Ontario, resulting in an incidence of 1.11 (0.63-1.79 per 1000 person-years which is exactly as ours (figure 5).

We found a higher SUDEP risk in the older age group than previously thought. Our results are in agreement with the opinion that the undercount of SUDEP might be great in older age groups (Thurman et al., 2014; Devinsky et al., 2016b). The higher occurrence of competing causes of death, lower autopsy rates among older persons, less documentation to be found regarding the circumstances of sudden death in the older age, all contribute to this under-ascertainment. This highlights the difficulties in obtaining a reliable assement of the SUDEP risk in older people.

6.2.2 Circumstances of SUDEP

Our results show that most SUDEP victims live alone or do not share a bedroom. This is line with a previous case-control study showing lack of night-time supervision as an important risk factor (Langan et al., 2005) and another study were SUDEP only occurred when children with severe epilepsy, enrolled at a special residential school, were on leave from the institution and did not have their regular supervision (Nashef et al., 1995).

Our results support further that SUDEP is a GTCS related event. In the MORTEMUS study (Ryvlin et al., 2013), all fatalities were preceded by a GTCS. In our study, all witnessed preceding seizures were GTCS. We were also able to compare definite SUDEP deaths to autopsied non-SUDEP deaths, when known, a GTCS preceded 21% among the witnessed deaths, while this was the case in 95% among the definite SUDEP cases. There were, however, five witnessed SUDEP cases in our series that were not preceded by a seizure. Although rare, this has been reported before (Lhatoo et al., 2016). This could imply at least two things. Firstly, that SUDEP can have a heterogeneous pathophysiology (Tomson et al., 2008). Secondly, sudden unexpected deaths occur in the general population, even though it is 24 times less common than in the epilepsy population. Hence, some sudden deaths in the epilepsy population may have no connection with the comorbid epilepsy.

Regarding seasonality of SUDEP, we did not observe a higher incidence during the winter months as in sudden cardiac death and Sudden Infant Death Syndrome (SIDS) (Douglas et al., 1998; Arntz et al., 2000; Gerber et al., 2006). This is in line with a SUDEP study from the UK which relied on death certificates only (Bell et al., 2010). Neither did we find an increased occurrence during morning hours or Mondays as in sudden cardiac deaths (SCD) (Arntz et al., 2000). As reported before (Lear-Kaul et al., 2005; Hitiris et al., 2007; Zhuo et

al., 2012; Clark and Riney, 2016) we found a clear preponderance for SUDEP to occur at night. Thus, SUDEP is predominately a GTCS and a night time related event and differs in many aspects from SIDS and SCD.

In the majority of SUDEP cases where body position was documented, they were found in the prone position. This is line with previous studies (Earnest et al., 1992; Kloster and Engelskjon, 1999; Opeskin and Berkovic, 2003; Liebenthal et al., 2015). Those who died at night were also more often found in the prone position than deaths occurring at other times and in our reference group of autopsied non-SUDEP the prone position was much less common than in the definite SUDEP group. The MORTEMUS study showed that many of the victims did not sleep in the prone position but shifted to that position during the seizure. Therefore, it is unlikely that campaigns promoting epilepsy patients to sleep on their back would be of any help. With this said it is possible that the position during a seizure can have a bearing on the final outcome and that simple interventions such as shifting the patient position and stimulation after the seizure could reduce the SUDEP risk (Nashef et al., 1995; Langan et al., 2005). This is still unproven but the use of a listening devise or regular checks during the night or shearing a room with an individual capable of giving assistance were associated with a markedly decreased risk SUDEP risk in one case-control study (Langan et al., 2005). There is a steady development in seizure alert alarms which might reduce SUDEP risk in the future (Ryvlin et al., 2018a). At the same time someone needs to be close by, respond and know how to reposition the patient, ensure that airways are not obstructed and possibly provide oxygen or suctioning (Devinsky et al., 2016a). This imposes challenges since the majority of Swedish SUDEP victims live alone.

6.2.3 Clinical risk factors and SUDEP risk

Our results confirm the main conclusion of the pooled analysis of four case-control studies (Hesdorffer et al., 2011) and the recent systematic review (Harden et al., 2017) that the presence and frequency of GTCS is by far the strongest risk factor for SUDEP. This applied also to nocturnal GTCS. In line with the previous pooled analysis of case-control-studies (Hesdorffer et al., 2011) we saw an incremental risk increase from no seizures up to 4-10 GTCS.

Previous studies have focused on GTCS or seizures as a whole but have not systematically analyzed non-GTCS. Therefore, is it an important result, that no increased SUDEP risk was seen in patients with only non-GTCS. This applied also to nocturnal non-GTCS. This has not been analyzed before to our knowledge (Nilsson et al., 1999; Walczak et al., 2001; Langan et al., 2005; Hitiris et al., 2007; Hesdorffer et al., 2011; Harden et al., 2017). This information is useful when counseling the individual patient. Complete seizure freedom cannot be expected in all patients, but it appears that much can be gained if focal seizures can be contained and prevented from evolving to bilateral tonic-clonic seizures.

VNS treatment was associated with a 59% risk reduction. These are interesting findings but due to the small numbers they should be interpreted with caution. The results aiming at assessing the effects of VNS on SUDEP risk have been somewhat conflicting (Annegers et al., 2000; Granbichler et al., 2015). This was addressed in a retrospective analysis of a large database of 40,443 patients with VNS therapy up ten years after implantation (Ryvlin et al., 2018b). In this cohort, the SUDEP risk was 25% lower during years 3-10 compared to the first two years. Despite large numbers, these findings need also to be interpreted with caution

due to the lack of a control group and the tendency for SUDEP incidence to decrease over time, as shown in a Swedish study (Tomson et al., 2018).

We observed as previous studies (Hesdorffer et al., 2011) that substance abuse and alcohol dependence, both which can lower the seizure threshold, increased the risk and should be taken into consideration when counseling the patient. Once we adjusted for GTCS frequency a number of formerly proposed risk factors (Nilsson et al., 1999; Walczak et al., 2001; Langan et al., 2005; Tomson et al., 2016), examples being age at onset, comorbid mental health disorders and use of antipsychotic drugs, were not associated with SUDEP. Furthermore, no increased risk was observed in those with a history of heart disease (arrythmias, heart failure, cardiomyopathy or ischemic heart disease) or chronic lower respiratory diseases or other neurological disorders.

In line with a previous report (Langan et al., 2005) of a protective effect of nighttime supervision (sharing a bedroom with someone capable of giving assistance or regular checks throughout the night or use of listening devices) and another study reporting SUDEP more common in an epilepsy center with less supervison at night (van der Lende et al., 2018), we saw a substantially greater SUDEP risk for those living alone, especially those not sharing a bedroom.

With interaction analysis we were able to demonstrate a supra-additive increase in SUDEP for those who have GTCS and sleep alone. Up to 69% of these deaths could possibly be prevented by removal of one of these risk factors. Sharing a room with someone is of course not always possible or desired and this highlights the dilemma between the wish to reduce SUDEP risk and the desire to live an independent life.

6.2.4 Pharmacological treatment, adherence and SUDEP risk

Our results on polytherapy are compatible with observations in a previous meta-analysis of placebo-controlled randomized trials investigating adjunctive AED treatment of pharmaco-resistant epilepsy (Ryvlin et al., 2011). In this meta-analysis, identifying 20 SUDEP cases (18 definite or probable), SUDEP was significantly less frequent in the group randomized to add-on with an AED at a presumed efficacious dose than in the add-on placebo group (Ryvlin et al., 2011). In contrast to our present study, data on seizure control in relation to SUDEP occurrence were not available in this meta-analysis. Our results that polytherapy reduces the risk for SUDEP together with Ryvlin's observations should encourage physicians to consider adding an AED in patients experiencing GTCS despite optimised monotherapy. Polytherapy was associated with reduced SUDEP risk even after adjustment for GTCS frequency. How polytherapy can reduce the risk for SUDEP beyond its effect on GTCS frequency is, however, unknown. One possibility is that polytherapy decreases the severity of the GTC with less impact on e.g. ascending and descending arousal systems. This could subsequently lead to less unresponsiveness and respiratory depression and reduced SUDEP risk.

No AED was associated with an increased SUDEP risk, neither before nor after adjusting for covariates. The results of the less frequently used AEDs, levetiracetam, oxcarbazepine, and topiramate, need to be interpreted cautiously given the smaller numbers and the corresponding wider confidence intervals. Interestingly, out of the different AEDs used in monotheraphy, the lowest risk was seen in users of levetiracetam, with an OR of 0.10. To our knowledge this finding has not been reported before. Levetiracetam has a mode of action different from other AEDs. Whether this relates to a particularly beneficial impact on SUDEP risk, remains to be explored.

Contrary to some other studies, we did not find an increased SUDEP risk in individuals taking carbamazepine (Timmings, 1993; Langan et al., 2005). One previous small case-control study has suggested an increased SUDEP risk specifically among female patients treated with lamotrigine (Aurlien et al., 2007), an observation that was not confirmed in the present study.

Compared to adherence, non-adherence was associated with a more than a threefold higher mortality in a retrospective cohort study from the US, where Medicaid claims data were used to evaluate adherence to treatment in epilepsy patients with AED prescriptions (Faught et al., 2008). A study from the UK, using similar methods as we, also found non-adherence to be associated with an increased mortality (Risdale et al., 2011). In both these studies the investigators analysed all-cause mortality and not SUDEP specifically. In our study, using physicians' mentioning of non-adherence in medical records yielded a threefold increased risk of SUDEP. We observed the same tendency when time since last dispensed AED exceeded 180 days in model 2, supporting the role of non-adherence as a risk factor for SUDEP. The high risk associated with GTCS and the risks associated with poor adherence should prompt physicians and patients to take measures to improve seizure control and facilitate adherence.

As mentioned before, data from people with epilepsy suggest that SSRIs are associated with reduced peri-ictal oxygen desaturation in focal seizures, but not in GTCS (Bateman et al., 2010). Moreover, pre-treatment with fluoxetine, an SSRI antidepressant prevented the postictal respiratory arrest and SUDEP in an animal seizure model (Tupal and Faingold, 2006). We did, however, not find a reduced risk of SUDEP with use of SSRI or other antidepressants. This is in line with a study which did not find evidence that SSRIs protected

against all-cause mortality in a large population-based cohort study of people with epilepsy (Josephson et al., 2017). Pharmacological treatment (beta blockers and statins) has been tried successfully in prevention of sudden cardiac death in patients with coronary artery disease, post myocardial infarction, structural heart disease and congestive heart failure (Arshad et al., 2008). Atypical and typical antipsychotics have been shown to increase mortality, including sudden cardiac death (Murray-Thomas et al., 2013). However, SUDEP risk has not been assessed in relation to beta blockers, statins, or neuroleptics before. We did neither observe an increased nor reduced SUDEP risk with concomitant use of neuroleptics or beta blockers, however, statin use was associated with a 66% reduced SUDEP risk even after adjusting for GTCS frequency. An association has been found between the use of statins and a reduced risk of developing epilepsy (Etminan et al., 2010) and intake of statins has been associated with reduced mortality in status epilepticus (Sierra-Marcos et al., 2015). There are also studies reporting statins to reduce the risk of sudden cardiac death (Beri et al., 2010), but ours is the first study to indicate a reduction in the risk of SUDEP.

6.3 METHODOLOGICAL ASPECTS

6.3.1 Strengths of the studies

The main strengths of our studies are their size and that they are nation- and population-based. Considering that the total Swedish population in 2002 was 8.925 million, and an estimated epilepsy prevalence of 0.6%, the 78,524 individuals identified in the SNPR during 1998–2005 most likely represent the vast majority of inhabitants with epilepsy. A further strength is the fact that the controls came from the same population as the cases, and that we were able to attain records for 97% of the 1275 potential controls and that we reviewed all deaths for one year (2008), with meticulous assessment of all relevant documentation for all potential SUDEP cases. Additionally, the validity of the epilepsy diagnosis was ascertained with chart review, and those not meeting the epilepsy criteria were excluded. It is therefore

likely that the results are representative for other countries with similar socioeconomic standards and healthcare systems. Another strength was that we used data from the Swedish Prescribed Drug Register which covers all prescriptions dispensed in pharmacies in Sweden, which is likely to be more accurate in terms of what the patient is realistically taking than information from patient records or prescription data from registries, as a measure of adherence. To our knowledge this methodology in combining extensive records review and registers has not been applied to this extent before in evaluating SUDEP risk.

6.3.2 Limitations of the studies

As described above, we assume that the majority of individuals with epilepsy between 1998-2005 were included in our study population. However, this is not known for certain since patients followed by family physicians who did not seek hospital during the eight-year period will not be included in the study population. It is conceivable that some milder cases of epilepsy were missed. We might therefore have underestimated the denominator somewhat and possibly overestimated the incidence of SUDEP, since the frequency of SUDEP is likely to be lower among people with milder forms of epilepsy. Since our review of medical charts, suggests that roughly 10% of the individuals in the study population do not have epilepsy, this would on the other hand have contributed to an overestimation of the denominator. Furthermore, our study was performed on a prevalent epilepsy population and did not specifically follow incident cases from their epilepsy onset. Some caution is therefore justified in attempts to apply our results on newly diagnosed epilepsies.

Misclassification of SUDEP is possible, not the least since it is a diagnosis of exclusion. Pitfalls include for example the possibility of patients having died from an unwitnessed status epilepticus. Furthermore, around half of our 329 SUDEP cases were not autopsied. This is the

reason we primarily included only definite and probable cases in the case-control study. We found a high concordance between the older classification (Annegers, 1997) and the more recent (Nashef et al., 2012).

Among the weaknesses are that the authors extracting information were not blinded to the outcome, and aware of previous reports on SUDEP risk factors, which may introduce bias. Furthermore, patient records have their inherent limitations, but we had relatively extensive records for both cases and controls and information was collected identically using a standardized protocol for both cases and controls. The registries used also have their limitations. Even though we found the ICD code for epilepsy to have a validity of 90% this does not necessary hold for other diagnoses used in the study.

With respect to living conditions, information was somewhat more extensive on the cases than controls due to additional information collected in conjunction with their death. With this said, information on living conditions was absent in only a small fraction of controls and should not have a major impact on our results. In reference to circumstances of death, another potential bias could be that it is easier for a witness to detect a GTCS than a non-GTCS and the latter can therefore go unnoticed.

Our definitions of being on an AED and adherent (AED dispensed within 90 days of death or index date) could be too strict. It is conceivably that patients had accumulated medications over time and have not dispensed AEDs or other medications within 90 days of death or index date without being non-adherent. This could possibly underestimate SUDEP risk in association to non-adherence. Additionally, dispensing medication does not guarantee intake. Furthermore, the prescription registry does not include those individuals living in an

institution which are for example common for chronic epilepsy patients in other countries. Since Sweden does not have such institutions and that very few cases or controls were admitted to hospital in the months leading up to death or index datum which could affect dispensing of drugs, it should not affect our results.

Our study was observational and therefore we cannot rule out confounding. This is of concern in paper III and IV where we aimed to identify risk factors for SUDEP. Even though we could adjust for a wide range of potential confounders, more than in any previous SUDEP study, there could be unknown confounders or residual confounding contributing to the observed associations. Moreover, some of the risk factors studied could be mediators, i.e. in the causal chain between the exposure and outcome. Furthermore, despite this being the largest SUDEP study until now, some analyses, e.g. those addressing individual AEDs and epilepsy surgery were hampered by small numbers, and wide confidence intervals. These findings should consequently be interpreted with caution.

7 CONCLUSION

More than one in every thousand epilepsy patients dies every year due to SUDEP and around 100 individuals in Sweden every year. SUDEP does not predominately affect young adults as thought before and it is evident that neither death certificates nor cause-of-death registries can be used for reliable monitoring of SUDEP incidence over time. GTCS, here including focal to bilateral as well as generalized tonic-clonic seizures, are indisputably a decisive risk factor for SUDEP for the following reasons; We found no increase in those with non-GTCS seizures alone; All seizures in conjunction with witnessed SUDEPs were GTCS and the majority of unwitnessed cases had indirect signs of a previous GTCS. We observed a gradual risk increase from having a history of GTCS, through the presence of GTCS and increased frequency of GTCS during the last year of observation. SUDEP is also obviously a night time and sleep related event considering that the majority died in bed at night. What makes SUDEP more susceptible to occur at night is not fully apparent. It could be the lack of supervision as indicated by our finding that not sharing a bedroom increased the SUDEP risk. Even though GTCS is a stronger risk factor, these two risk factors together evidently have a magnifying effect on each other since those with ≥4 GTCS who lived alone had an 82-fold increased risk for SUDEP. On the positive side, our findings indicate that 69% of SUDEPs could potentially be prevented if patients were free from GTCS or did not sleep alone. This and the protective effect of polytherapy has not been demonstrated before. Our results provide support for the importance of medication adherence and intensified AED treatment. The available evidence suggests that physicians may want to consider AED polytherapy more pro-actively for patients with poorly controlled GTCS. Finally, our findings did not support the previously suggested preventive role of SSRIs, while we found indications that statins might have a protective effect which needs to be researched further.

8 FUTURE PERSPECTIVES

Even though knowledge on the incidence, circumstances and risk factors in SUDEP has improved with this study, a number of challenges remain and should be considered for future studies. Regarding seizure control and SUDEP risk, studies are needed that differentiate between focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures. Studies are also needed that aim to clarify by what mechanisms AEDs reduce SUDEP risks apart from reducing frequency of GTCS. Considering the importance of living conditions, it would be interesting to compare SUDEP incidence in communities where living condition are different, e.g. comparing the SUDEP incidence in Sweden with that in societies where living alone is less prevalent and where people with severe epilepsy are more likely to live in residential care.

Independent studies are needed to confirm or refute the observed differences between AEDs and the apparent protective effect of statins. Future intervention studies aiming at assessing potential preventive measures could consider in addition to pharmacological interventions, systematic efforts to enhance adherence, effectiveness of different seizure detection alarms and other monitoring systems. Further refinement of individual SUDEP risk estimates would be of value both for patient counselling and for the selection of patients for intervention studies. Methods need to be developed that permit surveillance of SUDEP incidence over time in large populations and that ideally are applicable across countries. This would be important from a public health perspective, but also for future intervention studies.

9 ACKNOWLEDGEMENTS

Professor **Torbjörn Tomson**, my supervisor, friend and tennis partner. Besides being able to discuss politics, literature and sports it has been an honor to have you as a supervisor, an international authority in the field. Through working with you I have gained an insight into how things should be done properly, which I will carry with me forever. Thank you for your guidance and generous support over the years. Your intellectual sharpness is second to none. You have been great. Thank you.

Docent **Sofia Carlsson**, my co-supervisor, it has been a great pleasure to work with you. You always come with new and constructive points to improve the work. Your deep epidemiological knowledge has greatly improved this work.

Docent **Peter Mattsson**, my co-supervisor, thank you for your sharp analyses, your wide knowledge in neurology and coming regularly to Stockholm.

Tomas Andersson, thank you for your patience, without your statistical expertise this work had been difficult to complete.

Magnus Andersson, my mentor. Thanks for hiring me, for a much-cherished friendship and deepening my relationship with Bob.

My previous clinical supervisor, **Björn Hedman**, thank you taking care of me when I was new in Sweden and for being "språkpolis", when needed.

My good friends in the MSLB ("män som läser böcker"): **Anders, Erik and Mathias.**

Over my 12 years at the department of Neurology, I have had the pleasure to work some fantastic colleagues at the Neurology department especially: **Fredrik, Faiez, Lou, Albert, Ellen, Tomas, Anne, Karin, Christina, Anders S, Lars-Olof, Per, Maria, Ritva, Henrik,**

Charith, Mohsen, Martin, Einar, Michael, Tiago, Anna, Lisa, Liisa, Benno, Sofia, Giuseppe, Sebastian, among many others.

My good Icelandic colleagues and friends in Stockholm, some living in Iceland now: **Gylfi, Þorgeir, Snjólaug, Bjarni, Dagur, Kristján, Elín, Lóa, Björn, Þórir, Helgi, Halldór, Margét, Hildur, Bille, Pontus, Sigurður Yngvi, Jóhann, Sigríður, Páll, Hilmir, Kolbeinn, Börkur** among many others.

Thank you to **Åsa, Christina, Gretel, Åke och Gunilla** for all your help.

My friends in Frösunda: **Megan, Dave, Simon and Jesika** and your wonderful children

My good friends and colleagues in Iceland: **Ingvar, Haukur, Elfar, Elías, Ágúst,** among many others.

My dear family: **my mother and father, sisters, parents in law**, my children (**Helgi, Anna and Sveinn**) but above all my wife **Inga**. This thesis is dedicated to you. Thank you for everything.

10 REFERENCES

Adelöw C, Andell E, Amark P, Andersson T, Hellebro E, Ahlbom A, Tomson T. Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden: First report from the Stockholm Incidence Registry of Epilepsy (SIRE). Epilepsia 2009;50(5):1094-101.

Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. European journal of epidemiology 2005;20:575-579.

Annegers IF. United States Perspective on Definitions and Classifications. Epilepsia 1997;38 (Suppl. 11): S9-S12.

Annegers JF, Coan SP, Hauser WA, et al. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia 2000;41:549–53.

Arntz HR, Willich SN, Schreiber C, et al. Diurnal, weekly and seasonal variation of sudden death. Population-based analysis of 24,061 consecutive cases. Eur Heart J 2000;21:315–320.

Arshad A, Mandava A, Kamath G, Musat D. Sudden cardiac death and the role of medical therapy. Progr Cardiovasc Dis 2008;50:420-438.

Aurlien D, Tauboll E, Gjerstad L. Lamotrigine in idiopathic epilepsy - increased risk of cardiac death? Acta Neurol Scand 2007;115:199-203.

Bagnall RD, Crompton DE, Petrovski S, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. Ann Neurol. 2016;79:522–34.

Bateman LM, Li CS, Lin TC, Seyal M. Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. Epilepsia 2010; 51: 2211–14.

Bell GS, Peacock JL, Sander JW. Seasonality as a risk factor for sudden unexpected death in epilepsy: a study in a large cohort. Epilepsia 2010;51:773-6.

Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia 2010;51(4):671-675.

Beghi E, Giussani G, Sander JW. The natural history and prognosis of epilepsy. Epileptic Disord 2015;17(3):243-253.

Berg AT, Nickels K, Wirrell EC, et al. Mortality risks in new-onset childhood epilepsy. Pediatrics 2013; 132: 124–31.

Beri A, Contractor T, Khasnis A, Thakur R. Statins and the reduction of sudden cardiac death: antiarrhythmic or anti-ischemic effect? Am J Cardiovasc Drugs 2010;10(3):155-64.

Clark D, Riney K. A population-based post mortem study of sudden unexpected death in epilepsy. J Clin Neurosci 2016;23:58-62.

Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol 2016a; 15:1075–88.

Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: A call for action. Neurology 2016b;86(8):779-86.b)

Devinsky O, Friedman D, Duckrow RB, et al. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. Epilepsia. 2018;59:555–61.

Dlouhy BJ, Gehlbach BK, Richerson GB. Sudden unexpected death in epilepsy: basic mechanisms and clinical implications for prevention. J Neurol Neurosurg Psychiatry 2016;87:402–13.

Donner EJ, Smith CR, Snead OC 3rd. Sudden unexplained death in children with epilepsy. Neurology 2001;57:430–34.

Earnest MP, Thomas GE, Eden RA, et al. The sudden unexplained death syndrome in epilepsy: demographic, clinical and post-mortem features. Epilepsia 1992;33:310–6.

Etminan M, Samii A, Brophy JM. Statin use and risk of epilepsy: A nested case‐control study. Neurology 2010;75:1496‐500.

Fazel S, Wolf A, Langstrom N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet 2013; 382: 1646–54.

Faught E, Duh MS, Weiner JR, Guérin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. Neurology 2008;71(20):1572-8.

Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy. A systematic review and meta-analysis of international studies. Neurology 2017;88:1-8.

Fisher RS, Boas WV, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46:470–472.

Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. Epilepsia 2014;55(4):475–482.

Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017a;58:522-530.

Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017b;58(4):531-542.

Ficker DM, So EL, Annegers JF, O'Brien PC, Cascino GD, Belau PG. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology 1998; 51: 1270–74.

Forsgren L. Prevalence of epilepsy in adults in northern Sweden. Epilepsia 1992;33:450–458.

Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia 1996; 37:224–229.

Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe: a systematic review. Eur J Neurol 2005;12:245-253.

Forsgren L, Sundelin H, Sveinsson O. Epilepsy: incidence, prevalence and causes. Swedish medical journal 2018;21;115.

Garwood F. Fiducial limits for the Poisson distribution. Biometrika 1936;28:437–442.

Glasscock E. Genomic biomarkers of SUDEP in brain and heart. Epilepsy Behav 2014;38:172–9.

Granbichler CA, Nashef L, Selway R, et al. Mortality and SUDEP in epilepsy patients treated with vagus nerve stimulation. Epilepsia 2015;56:291–6.

Harden C, Tomson T, Gloss D, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017;88:1674–1680.

Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc 1996;71(6):576-586.

Hennessy MJ, Langan Y, Elwes RD, et al. A study of mortality after temporal lobe epilepsy surgery. Neurology 1999;53:1276-1283.

Hesdorffer DC, Benn EK, Cascino GD, Hauser WA. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. Epilepsia 2009;50 (5): 1102-8.

Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011; 52: 1150–59.

Hesdorffer DC, Tomson T, Benn E, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia 2012; 53: 249–52.

Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: A search for risk factors. Epilepsy Behav 2007;10:138-41.

Holst AG, Winkel BG, Risgaard B, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia 2013; 54: 1613–20.

Josephson CB, Gonzalez-Izquierdo A, Denaxas S, Fitzpatrick NK, Sajobi TT, Engbers JDT, Patten S, Jette N, Wiebe S.Serotonin reuptake inhibitors and mortality in epilepsy: A linked primary-care cohort study. Epilepsia 2017; 58(11):2002–2009.

Keller AE, Whitney R, Li SA, Pollanen MS, Donner EJ. Incidence of sudden unexpected death in epilepsy in children is similar to adults. Neurology 2018;91: e107–e111.

Kloster R, Engelskjon T. Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. J Neurol Neurosurg Psychiatry 1999;67:439–44.

Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. Epilepsia 2012; 53: 253–57.

Langan Y. The incidence of sudden unexpected deaths in epilepsy in South Dublin and Wicklow. Seizure 1998; 7: 355-358.

Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005; 64: 1131–33.

Lear-Kaul KC, Coughlin L, Dobersen MJ. Sudden unexpected death in epilepsy: a retrospective study. Am J Forensic Med Pathol 2005;26:11–17.

Leestma JE, Walczak T, Hughes JR, Kalelkar MB, Teas SS. A prospective study on sudden unexpected death in epilepsy. Ann Neurol 1989;26:195-203.

Lhatoo SD, Nei M, Raghavan M, et al. Nonseizure SUDEP: Sudden unexpected death in epilepsy without preceding epileptic seizures. Epilepsia 2016;57:1161–1168.

Li R, Buchanan GF. Scurrying to Understand Sudden Expected Death in Epilepsy: Insights From Animal Models. Epilepsy Curr 2019;19(6):390-396.

Liebenthal JA, Wu S, Rose S, et al. Association of prone position with sudden unexpected death in epilepsy. Neurology 2015;84:703–9.

Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.

Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol 2019;34:423-437.

Massey CA, Sowers LP, Dlouhy BJ, et al. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. Nat Rev Neurol 2014;10:271–82.

McKee JR, Bodfish JW. Sudden unexpected death in epilepsy in adults with mental retardation. Am J Ment Retard 2000;105:229-35.

Mohanraj R, Norrie J, Stephen LJ, Kelly K, Hitiris N, Brodie MJ. Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study. Lancet Neurol 2006; 5:481-7.

Monté CP, Arends JB, Tan IY, Aldenkamp AP, Limburg M, de Krom MC. Sudden unexpected death in epilepsy patients: Risk factors. A systematic review. Seizure 2007;16(1):1-7.

Morton B, Richardson A, Duncan S. Sudden unexpected death in epilepsy (SUDEP): don't ask, don't tell? J Neurol Neurosurg Psychiatry 2006;77(2):199-202.

Mueller SG, Nei M, Bateman LM, et al. Brainstem network disruption: A pathway to sudden unexplained death in epilepsy? Hum Brain Mapp 2018;39(12):4820-4830.

Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis of the Global Burden of Disease study 2010. Lancet 2012;380(9859): 2197-2223.

Murray-Thomas T, Jones ME, Patel D, et al. Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: A study with the general practice research database. Cardiovasc Psychiatry Neurol 2013:247486.

Nashef L, Sander JWAS, Fish DR, Shorvon SD. Incidence of sudden unexpected death in an adult outpatient cohort with epilepsy at a tertiary referral center. J Neurol Neurosurg Psychiatry 1995; 58: 462-4.

Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia 1997; 38 (Suppl. 11), S6-S8.

Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012; 53: 227–33.

Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology 2011;77:1005-1012.

Nilsson L, Tomson T, Persson PG, Diwan V, Farahmand BY. Cause specific mortality in epilepsy - a cohort study of more than 9000 patients once hospitalized for epilepsy. Epilepsia 1997;38:1062-1068.

Nilsson L, Persson PG, Tibblin I, Farahmand BY. Tomson T. Risk factors for sudden unexpected death in epilepsy- a case-control study. Lancet 1999;353:888-93.

Nilsson L, Bergman U, Diwan W, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case-control study. Epilepsia 2001;42:667-73.

Opeskin K, Berkovic SF. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. Seizure 2003; 12: 456–64.

Patodia S, Somani A, O'Hare M, et al. The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy. Brain 2018;141(6):1719-1733.

Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. Epilepsy Res 2003;57:69-75.

Richerson GB, Boison D, Faingold CL, et al. From unwitnessed fatality to witnessed rescue: Pharmacologic intervention in sudden unexpected death in epilepsy. Epilepsia 2016;57(Suppl 1):35-45.

Ridsdale L, Charlton J, Ashworth M, Richardson MP, Gulliford MC. Epilepsy mortality and risk factors for death in epilepsy: a population-based study. Br J Gen Pract 2011 May;61(586):e271-8.

Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol 2011; 10: 961–68.

Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013; 12: 966–77.

Ryvlin P, Ciumas C, Wisniewski I, Beniczky S. Wearable devices for sudden unexpected death in epilepsy prevention. Epilepsia 2018a;59(suppl 1):61–66.

Ryvlin P, So EL, Gordon CM, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia 2018b;59:562–72.

Ryvlin P, Rheims S, Lhatoo SD. Risks and predictive biomarkers of sudden unexpected death in epilepsy patient. Curr Opin Neurol 2019;32(2):205-212.

Sander JW. Some aspects of prognosis in the epilepsies: a review. Epilepsia 1993;34(6):1007-1016.

Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–521.

Schraeder PL, Delin K, McClelland RL, So EL. A nationwide survey of the extent of autopsy in sudden unexplained death in epilepsy. Am J Forensic Med Pathol 2009; 30: 123–26.

Sierra‐Marcos A, Alvarez V, Faouzi M, et al. Statins are associated with decreased mortality risk after status epilepticus. Eur J Neurol 2015;22:402‐5.

Sidenvall R, Forsgren L, Blomquist HK, Heijbel J. A community-based prospective incidence study of epileptic seizures in children. Acta Paediatr 1993;82(1):60-5.

Sillanpää M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. N Engl J Med 1998;338(24):1715-22.

Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. N Engl J Med 2010;363(26):2522-9.

Sing A, Trevick S. The epidemiology of global epilepsy. Neurol. Clin 2016;34:837-847.

Sperling MR, Harris A, Nei M, Liporice JD, O'Connor MJ. Mortality after epilepsy surgery. Epilepsia 2005;46(Suppl 11):49-53.

Spratling WP. Prognosis. In: Epilepsy and its treatment. Philadelphia: W B Saunders, 1904: 304.

Surges R, Adjei P, Kallis C, et al. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: a case-control study. Epilepsia 2010;51:233–242.

Surges R, Strzelczyk A, Scott CA, et al. Postictal generalized electroencephalographic suppression is associated with generalized seizures. Epilepsy Behav 2011;21:271–4.

Syvertsen M, Nakken KO, Edland A, et al. Prevalence and etiology of epilepsy in a Norwegian county – a population based study. Epilepsia 2015;56:699-706.

Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: Assessing the public health burden. Epilepsia 2014; 55: 1479–85.

Thurman DJ, Logroscino G, Beghi E, et al. The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia 2017;58(1):17-26.

Téllez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. Epilepsy Res 2005;65:101-15.

Timmings PL. Sudden unexpected death in epilepsy: a local audit. Seizure 1993; 2:287-290.

Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurol 2008;7(11):1021-31.

Tomson T, Hirsch LJ, Friedman D, et al. Sudden unexpected death in epilepsy in lamotrigine randomized-controlled trials. Epilepsia 2013;54:135–140.

Tomson T, Surges R, Delamont R, Haywood S, Hesdorffer DC. Who to target in sudden unexpected death in epilepsy prevention and how? Risk factors, biomarkers, and intervention study designs. Epilepsia 2016; 57 (suppl 1): S4–16.

Tomson T, Sveinsson O, Carlsson S, Andersson T. Evolution over time of SUDEP incidence: A nationwide population-based cohort study. Epilepsia 2018;59(8):e120–e124.

Tupal S, Faingold CL. Evidence supporting a role of serotonin in modulation of sudden death induced by seizures in DBA/2 mice. Epilepsia 2006; 47;21-26.

van der Lende M, Hesdorffer DC, Sander JW, Thijs RD. Nocturnal supervision and SUDEP risk at different epilepsy care settings. Neurology 2018;91:e1508–e1518.

Vandenbroucke JP, Pearce N. Case-control studies: basic concepts. Int J Epidemiol 2012;41:1480–1489.

Vilella L, Lacuey N, Hampson JP, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). Neurology 2019;92(3):e171-e182.

Walczak TS, Leppik IE, D'Amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001;56(4):519-25.

Weber P, Bubl R, Blauenstein U, Tillmann BU, Lutschg J. Sudden unexplained death in children with epilepsy: a cohort study with an eighteen-year follow-up. Acta Paediatr 2005; 94: 564–67.

WHO. The World Health Report. Geneva 2000.

Zhuo L, Zhang Y, Zielke HR, et al. Sudden unexpected death in epilepsy: evaluation of forensic autopsy cases. Forensic Sci Int 2012;223:171–175.